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## PATHOGENESIS OF INTESTINAL AMEBIASIS IN KITTENS<sup>†</sup>

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The principal object of the observations and experiments recorded in this paper was to learn the nature of the attack of *Endameba histolytica* on the colon in kittens. Since, therefore, the emphasis is placed on the origin and the development of the lesions, the term "pathogenesis" is used rather than "pathology."<sup>1</sup> Pathogenesis also concerns the effects on the parasite of the reactions of the host. Evidences of this reaction may be studied in the endamebas because their nuclei, like those of the body cells, pass through various stages of necrosis after death. The plan of procedure was to inoculate kittens in several well tested ways, to kill them at intervals of from eighteen hours to thirty days afterward, to fix the tissues of the colon and to section and stain them. The limitations of this method, particularly in the field of pathogenesis, were clearly recognized. One had to draw conclusions from the appearance of fixed material as to the reaction that had occurred during life. As the work progressed, it was found practicable to study the lesions in the living colon for a short time after its removal from the body. It is hoped that other ways of using living material may soon be devised.

The problem was suggested by Dr Robert Hegner. Laparotomies were performed on the kittens, as one method of infecting them. A technic developed and demonstrated by Dr Justin Andrews was used. It involved the use of sterilized instruments, towels, gauze, tape, and other such paraphernalia, and aseptic precautions. The kittens recovered quickly, and there was seldom any peritonitis.

### REVIEW OF THE LITERATURE

The susceptibility of the kitten to amebiasis following rectal injection of material from human dysenteric stools was demonstrated by Hlava.<sup>2</sup>

<sup>†</sup> Submitted for publication, June 18, 1928.

<sup>1</sup> From the Department of Protozoology of the Johns Hopkins University School of Hygiene and Public Health. This investigation is part of a series on host-parasite relations aided by a grant from the Committee on Scientific Research of the American Medical Association.

1 "Pathogenesis has reference to the generation and development of disease"—Encyclopedia Britannica. "Pathological disturbances are the result of some form of injury or of the immediate or more remote reactions of the body to injury"—MacCallum, 1925.

2 Hlava. Dysenterie in Bohemia (article in Bohemian), abstract in Centralblatt Bacteriol 1 537, 1887.

Late<sup>1</sup> investigations established the following facts (1) the non-pathogenicity for kittens of the bacterial flora of these dysenteric stools (Kartulis<sup>3</sup>), (2) the noninfectivity, when administered via the mouth, of dysenteric feces containing trophozoites but not cysts (Quincke and Roos<sup>4</sup>), (3) the pathogenicity of endamebas from bacteria-free abscesses of the human liver (Kruse and Pasquelle<sup>5</sup>), (4) the production of amebic abscesses of the liver in kittens (Marchioux<sup>6</sup>), (5) the occurrence in the human bowel of several species of endamebas, some pathogenic in kittens and others not so (Schaudinn,<sup>7</sup> Craig,<sup>8</sup> 1905, Viereck<sup>9</sup>), (6) the maintenance of viability and pathogenicity by *E histolytica* when passed through a series of kittens (Wenyon,<sup>10</sup> and Dale and Dobell<sup>11</sup>), (7) the invasion of the blood stream of cats infected with amebiasis by bacteria (Sellards and Baetjer<sup>12</sup>), (8) the excystation of the parasite in the colon when the cysts are injected through its wall following a laparotomy in which stasis is produced by a ligature (Sellards and Theiler<sup>13</sup>) It is also agreed that the kitten does not harbor endamebas except when experimentally infected, and that cysts are never produced in the colon of the cat, so that the latter never becomes a carrier Attempts to determine the occurrence or non-occurrence of diverse strains of *E histolytica*, some extremely pathogenic in cats and others not so, have led to conflicting views

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3 Kartulis, S Ueber tropische Leberabscesse und ihr Verhältniss zur Dysenterie, Virchows Arch f path Anat **118** 97, 1889, Ueber weitere Verbreitungsgebiete der Dysenterie Amoeben, Centralbl f Bacteriol **7** 54, 1890, Einiges ueber die Pathogenesse der Dysenterie Amoeben, *ibid* **9** 365, 1890

4 Quincke, H, and Roos, E Ueber Amoeben Enteritis, Berl klin Wchnschr **30** 1089, 1893

5 Kruse, W, and Pasquelle, A Untersuchungen ueber Dysenterie und Leberabscess, Ztschr f Hyg u Infectiouskrankh **10** 161, 1894

6 Marchioux E Note sur la dysenterie des pays chauds, Compt rend Soc de biol **51** 870, 1899

7 Schaudinn, F Untersuchungen ueber die Fortpflanzung einiger Rhizopoden, Arb a d Gsndhtsamte **19** 548, 1903

8 Craig, C F Entamoeba coli and Entamoeba dysenteriae, Am Med **9** 854, 897, 936, 1905

9 Viereck, H Studien ueber die in der Tropen erworben Dysenterie, Arch f Schiffs- u Tropen-Hyg **11** 1 (suppl) 1907

10 Wenyon, C M Experimental Amoebic Dysentery and Liver Abscess in Cats, J London Sch Trop Med **2** 27, 1912

11 Dale, H, and Dobell, C Experiments in the Therapeutics of Amebic Dysentery, J Pharmacol & Exper Therap **10** 399, 1917

12 Sellards, A W, and Baetjer, W A The Behavior of Amoebic Dysentery in Lower Animals and Its Bearing upon the Interpretation of Clinical Symptoms of the Disease in Man, Bull Johns Hopkins Hosp **25** 238, 1914

13 Sellards, A W, and Theiler, M Investigations Concerning Amoebic Dysentery, Am J Trop Med **4** 309, 1924

(Brumpt,<sup>14</sup> Wagener and Thompson,<sup>15</sup> Kessel<sup>16</sup> and others) Dobell and Laidlaw<sup>17</sup> claim to have developed a noninfective strain in culture by adding rice starch. This was accomplished after thirteen subcultures over a period of thirty-eight days. I<sup>18</sup> was unable to confirm these results.

It is generally agreed that the age during which kittens are most susceptible extends from the time of weaning to the attainment of a weight of from 600 to 700 grams. Investigators report from 50 per cent to 75 per cent of cats positive during this period. Unweaned kittens and older cats are rather refractive. If infection occurs in older cats, it is usually mild and the animal recovers (Sellards and Leiva<sup>19</sup>).

Boeck and Drbohlav<sup>20</sup> conducted a series of experiments which demonstrated that the cultivation of *E. histolytica* in vitro is a relatively simple procedure. This work is of outstanding importance. It relieves the experimenter of dependence on a haphazard supply of the parasite. As pointed out by Wenyon,<sup>21</sup> the aforementioned experiments also enforced a change of viewpoint concerning the pathogenicity of *E. histolytica*. It was formerly thought that the organism could not long endure without access to living tissues. More recent work (Dobell and Laidlaw<sup>17</sup> and Yorke and Adams<sup>22</sup>) has shown that the phenomena of encystment and excystation, which complete the known life cycle, may occur in the test tube.

Studies of the clinical course of amebiasis in kittens and of its pathology have not in any instance been adequately pursued. Controls were never kept, though the kittens were usually purchased in the streets. Such animals are undernourished and usually heavily infected with nematodes, cestodes, coccidia and ectoparasites. Kittens are subject

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14 Brumpt, E. Etude sommaire de l'*Entamoeba dispar* n. sp. amibe a Kystes quadrinuclees parasite de l'homme, Bull. Acad. de med., Paris **94** 943, 1925.

15 Wagener, E. H., and Thompson, M. Experimental Amoebiasis in Cats from Acute and Chronic Human Cases, Univ. California Pub. Zool. **26** 267, 1924.

16 Kessel, J. F. Amoebiasis in Kittens Infected with Amoebae from Acute and "Carrier" Human Cases and with Tetranucleate Amoebae of the Monkey and of the Pig, Am. J. Hyg. **8** 311, 1927.

17 Dobell, C., and Laidlaw, P. P. On the Cultivation of *Endamoeba histolytica* and Some Other Entozoic Amoebae, Parasitology **18** 283, 1926.

18 Rees, C. W. The Infectivity and Pathogenicity of a Starch-Fed Strain of *Endamoeba histolytica*, J. Parasitol. (to be published).

19 Sellards, A. W., and Leiva, L. Investigations Concerning the Treatment of Amoebic Dysentery, Philippine J. Sc. **22** 1, 1923.

20 Boeck, W. C., and Drbohlav, J. The Cultivation of *Endamoeba histolytica*, Am. J. Hyg. **5** 371, 1925.

21 Wenyon, C. M. Protozoology, New York, 1926.

22 Yorke, W., and Adams, A. R. D. Observations on *Endamoeba histolytica*, Ann. Trop. Med. **20** 279, 1926.



to pneumonia and bacillary dysenteries, particularly during the period when most susceptible to amebic dysentery. And yet it appears from the protocols that careful examinations of the contents of the stomach and the small intestines were not made. The aforementioned parasites were not noted as being present. Small kittens adapt themselves poorly to solitary confinement in wire cages, frequently the controls die, sometimes before the experiments are under way.

The foregoing review of experimental amebiasis in kittens is given because a statement of the present status of the disease is indicated in order to show the bearing on it of the work here set forth. In the field of pathogenesis, as the term is defined in this article, one finds only theories. The first was proposed by Schaudinn,<sup>7</sup> whose name *histolytica* suggests a cytolytin. He held that the penetration of the tissue is made possible for *E. histolytica* because the organism thrusts out, explosively, bladelike pseudopodia consisting only of ectoplasm, which are the weapons of attack. These organella differ from the blunt pseudopodia of *E. coli*, which are thrust out slowly and into which the endoplasm flows. Another theory by Councilman and Lafleur<sup>23</sup> and Wenyon (1912,<sup>10</sup> 1925<sup>21</sup>) presupposes that the trophozoites make their way to the fundi of the crypts of Lieberkuhn of the colon. Here they multiply. The gland responds by excessive secretion of mucus and becomes occluded. A cytolytic toxin secreted by the parasites causes necrosis of the epithelial cells of the gland, and thus an abscess is produced, consisting of a yellowish plug of necrotic material containing endamebas. By pressure and continued secretion, the endamebas may break through the muscularis mucosae into the submucosa, or the plug of necrotic material may be discharged, causing the flecks of bloody mucus which occur in the stools.

Dobell<sup>24</sup> described the earliest lesion as a hyperemic patch of the mucosa. The endamebas working in this area are the cause of this inflammation. They secrete a toxin which dissolves away the cells of the mucosa. In this way pools of cytolysed fluid are produced in which the amebas multiply. It is of interest in this connection that Craig<sup>25</sup> extracted a cytolytic substance in absolute alcohol from masses of *E. histolytica* grown in culture.

The theories are in conflict in essential particulars, though the last two agree in postulating some kind of secretion by the parasite. The

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23 Councilman, W. T., and Lafleur, H. A. Amoebic dysentery, Johns Hopkins Hosp. Rept. 2 293, 1891.

24 Dobell, C. Protozoal Diseases, in Byam and Archibald. Practice of Medicine in the Tropics, London, 1922, vol. 2, p. 1335.

25 Craig, C. F. Observations upon the Hemolytic, Cytolytic and Complement-Binding Properties of Extracts of *Endamoeba histolytica*, Am. J. Trop. Med. 7 225, 1927.

authors do not supply figures of the progressive stages in these processes or other adequate evidence to substantiate their theories. It seems obvious from this review that further research is indicated to determine to what extent any of the theories coincides with the facts.

#### MATERIAL AND METHODS

A strain of *E. histolytica* in culture obtained from Captain J. H. St. John of the Army Medical School, Washington, D. C., and established in this laboratory was available. It was cultivated in Boeck and Drbohlav's<sup>20</sup> egg slant serum.

TABLE 1—*Experiments with Laparotomy (The Endamebas Inoculated Were Cultured in Boeck & Drbohlav's Medium Without Starch)*

Kitten	Date of Operation		Subculture in Starch	Kitten's Weight, Gm	Fluid Injected, Cc	Lapse of Time, Hrs	Cat died (D) Cat Killed (K)	Degree of Infection	Character of Lesions
1*	Oct	4		600	0	44	K	+	None
2	Oct	19	2d	600	3	110	D	++	Mucosa necrotic, diphtheric membrane, nests of amebas in submucosa
3	Oct	22	3d	600	3	90	K	+++	Mucosa entirely necrotic, diphtheric membrane, submucosa greatly thickened and invaded
4	Oct	26	4th	610	3	27	K	+	Normal
5	Oct	30	6th	585	3	48	K	+++	Necrosis of superficial cells of mucosa over entire colon, submucosa thickened
6	Nov	3	8th	700	3	26	K	—	Normal, not sectioned
7	Nov	3	8th	450	1	27	K	—	Normal, not sectioned
8	Nov	3	8th	400	2	23	K	—	Normal, necrosis not demonstrable
9	Nov	3	8th	340	1	65	K	—	Lesions of mucosa not observable, submucosa thickened
10	Nov	3	8th	260	3	42	K	—	Normal, not sectioned
11	Nov	6	9th	320	5	90	D	+++	Necrosis of mucosa, few amebas, greatly thickened submucosa
12	Nov	6	9th	220	5	66	K	+	Normal, not sectioned
13	Nov	6	9th	340	5	18	D	—	Not sectioned
14	Nov	8	13th	800	5	42	K	+++	Necrosis of mucosa, diphtheric membrane, few amebas, thickened submucosa
15	Nov	8	13th	740	5	42	K	—	Normal, not sectioned
16	Nov	13	15th	920	5	40	K	—	Normal, not sectioned
17	Nov	13	15th	800	5	46	K	—	Normal, not sectioned
18	Dec	20	30th	400	5	65	D	+++	Necrotic mucosa, thickened submucosa
19	Dec	20	30th	400	5	91	K	—	Normal

\* No. 1 was treated exactly as were the others except that amebas were not injected.

medium. For the substratum used in the experiments listed in table 1, the medium was enriched with rice starch. The kittens were purchased on the streets. Well established methods of this laboratory were used in feeding and caring for them. Sanders<sup>20</sup> described these methods in detail.

As stated, one of the objectives of the experiments was to secure for study very early lesions in the mucosa of the colon. The method of laparotomy referred to was used for the experiments summarized in tables 1 and 2. After exposure of the colon, the latter was ligated near the rectum. By means of a Luer syringe, the culture fluid which contained amebas as well as yeasts and

26 Sanders, E. P. The Effects of Infection with *Endamoeba histolytica* on the Cells in the Blood of Kittens, in manuscript, 1928.

bacteria was injected through a no 1 hypodermic needle. The shock of the operation lowered the resistance of the kitten and the ligature prevented the voiding of the material, so that the amebas had a better chance of establishing themselves than when introduced into the open bowel. I<sup>28</sup> had demonstrated previously that the starch-fed amebas, referred to heretofore, are infective and pathogenic in kittens when the method of laparotomy is used. An objection

TABLE 2—*Experiments with Laparotomy (The Endamebas Inoculated Were Cultured in Boeck & Driehlav's Medium Without Starch)*

Kitten	Date of Operation	Kitten's Weight, Gm	Fluid Injected, Cc	Lapse of Time, Hrs	Cat Died (D) Cat Killed (K)	Degree of Infection	Character of the Lesions
18	Nov 17	260	5	22	K	+	No lesions showing amebas, colon poorly fixed
19	Nov 17	260	5	20	K	+	No lesions, no amebas in adherent mucus, colon poorly fixed
20	Nov 17	250	5	18	K	—	Colon was normal
21	Nov 18	840	5	42	K	+++	Generalized necrosis of mucosa inflammation and thickening of submucosa
22	Nov 18	920	5	18	D	+	Not sectioned, appeared normal
23	Nov 20	640	5	24	D	+	Localized lesions in the colon contained living amebas
24	Nov 22	1,200	5	23	K	++	Slight necrosis, no amebic lesions
25	Nov 21	1,250	5	26	K	—	Normal
26	Nov 22	1,500	5	18	D	—	Not sectioned, appeared normal
31	Nov 29	500	4	48	D	—	Not sectioned
41	Dec 6	1,260	5	72	K	+	Microscopic lesions near valve and ligature
45	Dec 6	1,100	5	73	K	—	Appeared normal, not sectioned
51	Jan 14	450	5	90	K	++	Small ulcer in cecum, otherwise no lesions
52	Jan 26	475	5	54	K	++	Picture similar to that in kitten 51, except that the lesion in the cecum was smaller
59	Feb 8	800	5	48	K	—	Normal
61	Jan 21	500	5	48	D	—	Not sectioned
62	Jan 21	520	5	72	D	+	Several ulcers
63	Feb 15	475	5	92	K	—	Normal
64	Feb 15	500	5	42	K	—	Normal
65	Feb 21	325	5	44	K	—	Normal
66	Feb 21	280	5	44	K	—	Normal
67	Feb 21	375	5	41	K	—	Normal
68	Feb 21	375	5	44	K	—	Normal
69	Feb 25	450	5	—	D	—	Accidentally killed during operation
70	Feb 25	500	5	46	K	++	One microscopic ulcer in cecum, otherwise normal
75	Feb 28	520	5	45	K	—	Normal
76	Feb 28	520	5	45	K	+++	One microscopic lesion near ileocecal valve, otherwise normal
77	Feb 29	750	5	64	K	+	Several small lesions, all contained amebas
78	Mar 8	450	5	42	D	—	Not sectioned
79	Mar 8	450	5	26	K	++++	Complete destruction of mucosa colon invested with diphtheric membrane
84	Mar 20	700	5	46	K	—	Normal
85	Mar 20	750	5	46	K	+	Normal
87	Mar 24	700	5	72	K	—	Normal

to this method was that pathologic conditions were induced by the operation per se independent of the lesions of amebiasis. Ample controls were maintained to demonstrate that the lesions resulting from the operation were not of a character to render the method unsuitable.

Infection of kittens was also accomplished by rectal injection. This method, well described in the literature, consisted of injecting the material by way of the anus through a rubber catheter into the colon. The anus was not subsequently closed. This procedure did not appreciably disturb the kitten or prevent the normal functioning of the bowel. Symptoms of dysentery

TABLE 3—*Experiments with Rectal Injection (The Endamebas Injected Were Cultured in Boeck & Dirlhlaes Medium Without Starch)*

Kitten	Kitten's Weight, Gm	Dates of Injections*	Probable Prepatent Period, Days	Symptoms	Date on Which Kitten Died (D), Was Killed (K), or Experiment Was Discontinued (D)	Degree of Infection	Character of Lesions
27	2,500	Nov 22, 26, 28, Dec 2, 9			Dec 27, I, D	—	Animal remained healthy
28	1,350	Nov 25, 28, 30			Dec 3, I, D	—	
30	400	Oct 10, 14, 19, 29, Nov 11 (P Nov 16)	5	Bloody mucus	Nov 26, K	—	Many masses adherent to mucosa, sections showed superficial necrosis, no amebae
31	530	Nov 20 (Dec 3 N), 19 parrot only			See table 2		
32	400	Nov 20			Nov 30, D	—	
33	640	Dec 1, 8	5	Bloody mucus, Dec 13	Dec 16, K	+	Bloody mucus in the jejunum, bacillary dysentery lesions distributed throughout the colon
34	510	Dec 1	2		Dec 9, D	—	Not sectioned because of autolytic changes
35	560	Oct 13, 14, Nov 17 (P 19)			Dec 2, K	+	Mucus patches adherent to mucosa, amebae not present in tissues
36		Dec 2			Dec 3, D	—	
37	440	Dec 2, 8			Dec 12, D	—	
38	400	Dec 2			Dec 1, D	—	Pneumonia
39	430	Dec 2			Dec 7, D	—	Pneumonia
40	1,120	Dec 5		Bloody mucus, Dec 17	Dec 20, D	—	Bloody mucus in the jejunum
42	1,320	Dec 5			Dec 12, I, D	—	
43	1,200	Dec 5			Dec 12, I, D	—	
44	650	Dec 5, 6		Bloody mucus, Dec 13	Dec 20, D	—	Bloody mucus in the jejunum
46	1,380	Dec 5			Dec 15, I, D	—	
48	540	Dec 9			Dec 12, D	—	Pneumonia
53	1,500	Jan 14			Jan 15, D	—	Pneumonia
56	900	Jan 14, 19		Bloody mucus, Jan 21	Jan 21, D	—	Bacillary dysentery
57	950	Jan 14, 18 (F)		Bloody mucus, Jan 21	Jan 21, D	—	Bloody mucus in jejunum
58	875	Jan 14, 19 (F)			Jan 21, D	+	Peritonitis
71	275	Feb 21, 27 (F) (P Feb 29)	1	Bloody mucus	Mar 5, K	+	Many shallow inflammatory lesions, many amebae in lesions
72	275	Feb 21, 23, 27 F (P Mar 1)	3		Mar 2, K	+	Lesions containing amebae not observable
73	250	Feb 21, 23, 27 F (P Feb 29)	2	Bloody mucus	Mar 3, K	++	Few lesions, much inflammation
74	275	Feb 21, 23, 27 F			Mar 2, K	—	Sections showed lesions containing E histolytica
78	450	Mar 2, 4, 6 (N 8)			See table 2		Table 2
79	450	Mar 2, 4, 6 (N 8)			See table 2		Table 2
80	400	Mar 6, 12, 19 F (P Mar 22)	3	Bloody mucus	Apr 13, D	++	Many lesions much necrosis, many amebae in lesions
81	400	Mar 6, 12, 19, 22 F (P Mar 24)	2		Apr 25, K	++	Multiple lesions general in distribution
82	400	Mar 6, 12, 19, 22 F (P Mar 24)	2	Bloody mucus	Apr 9, D		Sent to Kansas State University while infected
83	700	Mar 8, 12, 19, 22 F (P Mar 27)	5		Mar 27, K	+	Multiple lesions
84	700	Mar 8, 9 F, 12 (Mar 20 N)			Mar 20, see table 2		See table 2
85	750	Mar 8, 22 (20 N)			Mar 20, see table 2		See table 2
86	400	Mar 19, 22 F (29 N)			Mar 29, K		Colon lost
88	600	Mar 27 F, 29 F (P Apr 3)	5	Bloody mucus	Apr 10, K	++	Multiple lesions
89	600	Mar 27 F, 29 F (P Apr 2)	4	Bloody mucus	Apr 10, D	++	Multiple lesions few amebae in lesions

\* Key P = positive N = negative, F = feces from an infected kitten

always occurred in such kittens by the time that the fecal diagnosis was positive Table 3 shows that the animals were kept from four to thirty-four days, when killed, all of them showed lesions Some of these were as small as the smallest detectable lesions resulting from laparotomy Both sorts are described in the following matter under appropriate headings

One of the greatest difficulties was to locate the earliest lesions Little time could be given to the examination of the fresh colon because autolytic changes set in quickly One method finally devised was that of spreading the opened colon out in a petri dish, fixing it in hot Bouin's fluid for about half an hour or longer, then pouring the latter off and adding 70 per cent alcohol There was a hemorrhagic halo surrounding even the tiniest lesion, and the yellow color given by the picric acid caused this halo to stand out clearly when the tissue was examined under the binocular microscope Another method was that of sectioning the entire colon Only a small portion of the ribbon could be mounted, but the rest was preserved between sheets of paper, which were carefully labeled Cedar oil was used for clearing, and the sections were stained with iron hematoxylin and counterstained with eosin

#### GENERAL ANALYSIS OF THE EXPERIMENTAL DATA

Eighty-four kittens were used, and fifty-eight were of experimental value for this problem Thirteen died, either of bacillary dysentery or pneumonia or a complication of these diseases, during the latter part of November and December and January (table 3) These data indicated that kittens available from the streets in this climate during the aforesaid months are of lowered vitality and hence that other seasons of the year should be selected Five kittens were given over to other work because they had evidently developed the resistance that comes with age The data here presented agreed with those of other workers that unweaned kittens are also resistant to amebic infection Kittens 65, 66, 67 and 68 were unweaned and all were negative after laparotomy I was unable to infect eight other unweaned kittens, not listed in the tables, by the method of rectal injection None of the observed phenomena indicated any cause for the resistance of the older kittens, but there was evidence that something in the mother's milk protected suckling kittens from experimental amebiasis, as well as from other infections Kittens 71, 72, 73 and 74 were weaned in the laboratory They soon became infected after the change of diet

The colons of eight of the kittens that died during the night were not sectioned because of autolytic changes

Of forty-nine kittens inoculated after laparotomy, twenty-three gave positive reactions In nos 2, 3, 11 and 14, table 1, and in kitten 79, table 2, the lesions were severe The entire mucosa was necrotic and teeming with endamebas, and constituted a diphtheric membrane In kittens 2 and 3, table 1, the submucosa was also invaded The zone nearest the ligature was most severely affected But in nos 51, 52, 70, 76 and 77, the only lesions discernible occurred either in the cecum or near the ileocecal valve In kitten 41, there were small lesions near the

ileocecal valve and near the ligature as well. Extremely small lesions were demonstrated in kitten 41 (after seventy-two hours), kitten 70 (after forty-six hours) and kitten 76 (after forty-two hours). It was impossible to find amebic lesions at autopsy in eight of these that were infected or to demonstrate them in sections. A detailed description of the lesions with figures and a discussion is reserved for the following paragraphs.

Five of the twenty-six kittens of table 1 and table 2, found not to be infected at autopsy, died during the night. The colons of all the others appeared normal by macroscopic study. Tissues from the colons of fifteen were sectioned and studied microscopically. The vascular areas were somewhat hyperemic, but whenever conditions permitted the fixation of the colon immediately at death, the mucosa was normal. Number 87 of table 2 was kept seventy-two hours, no. 63 of table 2 ninety-two hours and no. 50 of table 1 ninety-one hours before autopsy, and in these as well as in most of the others, necrosis was not demonstrated. Figure 2 is a camera lucida drawing of the mucosa of the colon of kitten 50. All the kittens that were not infected, save kitten 1, received the same inoculum as those that were, as stated in the foregoing paragraphs; this material contained the amebas with an accompanying flora of yeasts and bacteria. The kittens that were not infected were treated the same in every other respect as those that were infected. It is therefore demonstrated that the lesions in the latter were due primarily to injury inflicted by *Endameba histolytica* and not to the operative procedure or to bacteria.

With four exceptions, nos. 30, 31, 33 and 35 of table 3, those treated by rectal injection, during November, December and January, were either age resistant or died before the experiments were concluded. Fifteen, all small kittens, were given injections during February and March; ten showed infection (table 3). Kitten 79 was counted infected because, despite a negative fecal diagnosis, it was later used for laparotomy and a diphtheric membrane developed in the colon in twenty-six hours, while the sister kitten treated likewise remained uninfected. It will be noted from table 3 that when fecal material from an infected kitten was used, infection followed much more often than after the use of amebas in culture fluid. This is evidence additional to that I<sup>18</sup> gave in a previous article that the chief factor in infectivity is the adjustment of the amebas to the environmental conditions in the colon of the kitten.

In none of the group listed in table 3 was the submucosa of the colon invaded. The lesions were usually widely distributed but were small, leaving the greater part of the mucosa still functional. The region about the ileocecal valve was the most severely injured in every case. Most investigators have reported death usually occurring in

kittens within from four to nine days after the end of the prepatent period. Especial reference may be made to Dale and Dobell (1917). But in this work no 80 lived twenty-four days and no 81, thirty-four days. All the others, except kitten 82, were killed though some were in a comatose condition. Number 82, which had withstood transfer to Kansas City while infected, lived sixteen days.

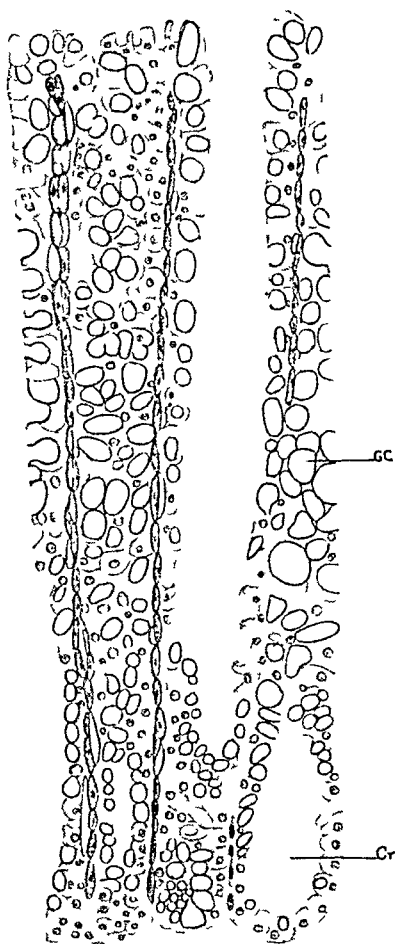


Fig 1—Camera lucida drawing of a section of the mucosa of a dysenteric colon of kitten 83 showing general enlargement of the crypts (*C*) and goblet cells (*GC*),  $\times 350$

#### DESCRIPTION OF THE LESIONS

In the unobstructed bowel the first symptom of intestinal amebiasis in the kitten was diarrhea. A copious secretion of the glands of the digestive tract must have occurred to produce the semifluid feces. The slides of the infected colons were therefore carefully studied and compared with those of the colons not infected in search of anatomic evidence of this hypersecretion. Figure 1 is a camera lucida drawing of

the mucosa of kitten 83, which was affected about seven days with dysentery (table 3). The crypts, it may be noted, are opened wide and the goblet cells are prominent, indicating that they were secreting actively when the kitten was killed. Sections through the colon of kitten 30 (table 3) showed the same characteristics as the tissue represented in figure 1, but lesions containing amebas could not be found. This kitten was heavily infected on November 16 and for at least a week thereafter, but infection was not present at autopsy on November 26. A similar condition was found in the colon of kitten 35 (table 3), although the latter did not show amebiasis at autopsy. Figure 2 is drawn from a

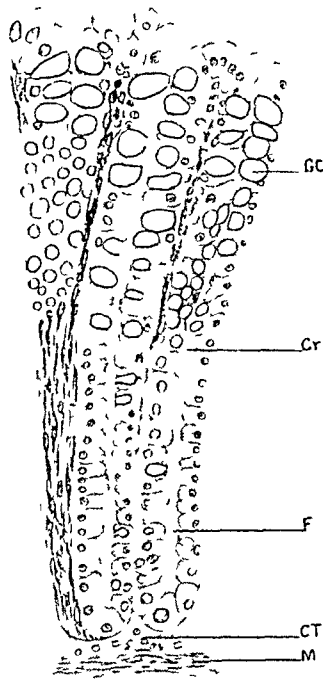


Fig 2—Camera lucida drawing of a section of the mucosa of the colon of kitten 50 killed ninety-one hours after inoculation by laparotomy and found negative for *Endameba histolytica*,  $\times 350$

Abbreviations Cr, crypt, C T, connective tissue, G C, goblet cell, F, fundus of the gland, M, muscularis mucosa

section of the mucosa of kitten 50 (table 2). This animal was kept ninety-one hours after a laparotomy, but amebas were not found. Evidences of dysentery in this colon were lacking, the mucosa appeared normal. In general, the sections showed that the condition represented in figure 1—that is, widely opened crypts and distended goblet cells—is a common characteristic of amebic dysentery in the kitten. In the early stages of the amebiasis, ulcers, if present were small—one had to search for them.



It was instructive to study the ulcers under the binocular microscope immediately after removal of the colon, while the latter was still living. To accomplish this, the colon was opened up in warm Locke's solution or normal sodium chloride, and the fecal material carefully washed away. The organ was then spread out in a petri dish in the same solution. The lesions appeared as hyperemic areas. When a bit of this tissue was teased out and mounted on a slide, it was seen under the compound microscope to contain numerous amebas. These were gorged with red blood cells and were in active locomotion. Therefore, some sort of injury had been inflicted which damaged the mucosa causing bleeding. The amebas profited by this injury, gaining a food supply of red blood cells.

Stained sections through ulcers containing amebas in twenty-four kittens were studied in several hundred slides. The general character of these lesions is indicated in tables 1, 2 and 3. It required over forty hours for the amebas to produce detectable ulcers after inoculation into a kitten by laparotomy. Ulcers could not be found in four kittens that were positive when killed after from twenty to twenty-seven hours, though in two of these cases, nos. 18 and 24, the entire colon was sectioned. No differences were observed between the early ulcers of six kittens infected by laparotomy and nine infected by rectal injection. In some of these early lesions, the epithelial cells of the mucosa were, for the most part, still intact (figs. 3, 6 and 7).

Figures 3, 4 and 5 are drawn from the colon of kitten 83, which was killed at the end of a five day prepatent<sup>27</sup> period following rectal injection. Figure 3 represents the entire lesion, while figure 5 shows in greater detail the group of amebas. Figure 4 is a diagram which indicates the relationship of the lesion to the mucosa as a whole, to the other tissues of the colon and to the lumen of the latter. In figure 3, it may be noted that there are two areas in which the cells of the lining mucous membrane are necrotic, also that the goblet glands are exceedingly prominent in adjacent cells that appear to be on the road to necrosis. Mucus and plasma appear to have enveloped and injured the attacking amebas. In the zone of necrosis deepest within the fold, there are evidences of an inflammatory reaction. Figure 5 shows the details of the nuclei of the amebas, some of which appear to be necrotic and others to be undergoing necrosis. The cytoplasm also appears vacuolated to an unusual degree.

Portions of early ulcers are pictured in figures 6 and 7. Figure 6 is a drawing from the outer margin of the only lesion that could be found

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<sup>27</sup> The "prepatent" period extends from the time the infective parasites enter the body of the host until their offspring can be recovered by specified laboratory methods. This period usually differs from the incubation period, the latter involves symptoms and is ordinarily longer.

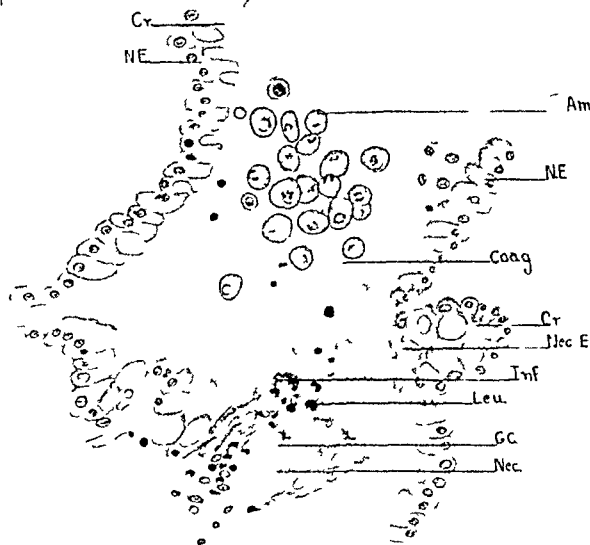


Fig 3—Camera lucida drawing showing a cluster of trophozoites of *E. histolytica* in a part of the lumen of the colon which is included within a fold of the mucosa. The outer layer of epithelial cells of the mucosa shows two necrotic areas,  $\times 175$

Abbreviations (figs 3 and 4) *Am*, amebas, *A P*, Auerbach's plexus, *Coag*, plasma and mucus coagulated by the fixative, *Cr*, crypt, *C M*, circular muscles, *G C*, goblet cell, *Inf*, zone of inflammation, *L*, lesion, *Leu*, leukocyte, *L M*, longitudinal muscles, *M*, mucosa, *N E*, normal epithelium, *Nec E*, necrotic epithelium, *Nec*, necrotic area of the mucosa, *S*, serosa

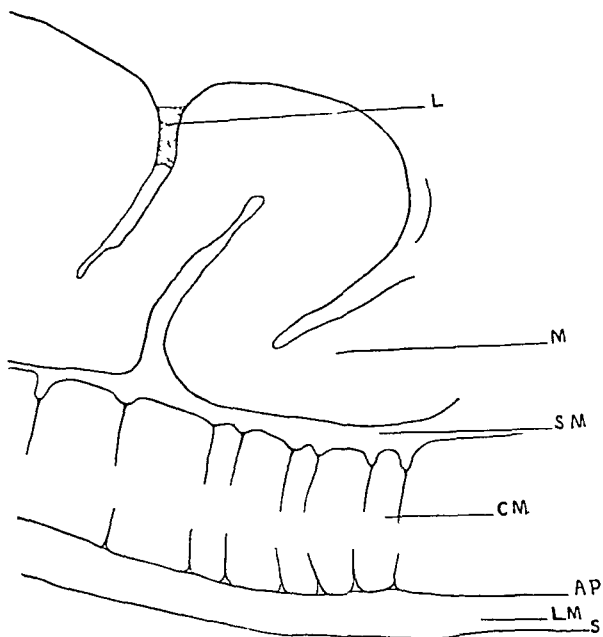


Fig 4—Outline of a section through the entire wall of the colon in which the lesion shown in figure 3 occurred, showing the location of the lesion and its relation to the other tissues of the colon,  $\times 16$

in kitten 70, killed forty-six hours after a laparotomy. Necrosis of the epithelium is seen in the area beginning at the reader's left. Throughout the lesions, necrosis did not extend more than for several cell layers in depth. The amebas are enveloped in what appears to be a fluid containing much cellular debris. A number of them appear to be in contact with normal epithelial cells. Figure 7 pictures the beginning of an inflammatory reaction in a zone between two crypts that is made up largely of connective tissue. This drawing is from a lesion in kitten 76, killed forty-five hours after laparotomy.

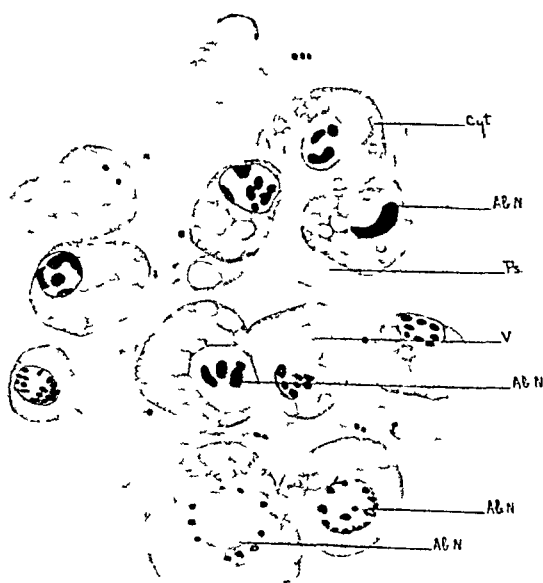


Fig 5—Camera lucida drawing of a portion of the lesion represented in figures 3 and 4, showing a group of *Endameba histolytica* with abnormal nuclei,  $\times 800$

Abbreviations Ab N, abnormal nuclei, Cyt, cytoplasm, Ps, pseudopodium, V, vacuoles

Figure 8 portrays an ulcer in the colon of kitten 41, killed seventy-two hours after laparotomy. In this lesion, the amebas were separated from intact epithelium by a zone of necrosis and plasma. It appears remarkable if so much destruction as is shown here was produced by the few amebas present. This ulcer occurred near the ligature that was tied around the colon near the rectum. Another ulcer, slightly more advanced, occurred in this colon near the ileocecal valve, but otherwise the mucosa was normal. It appears plausible that this ulcer may have been produced by a cytolytic toxin.

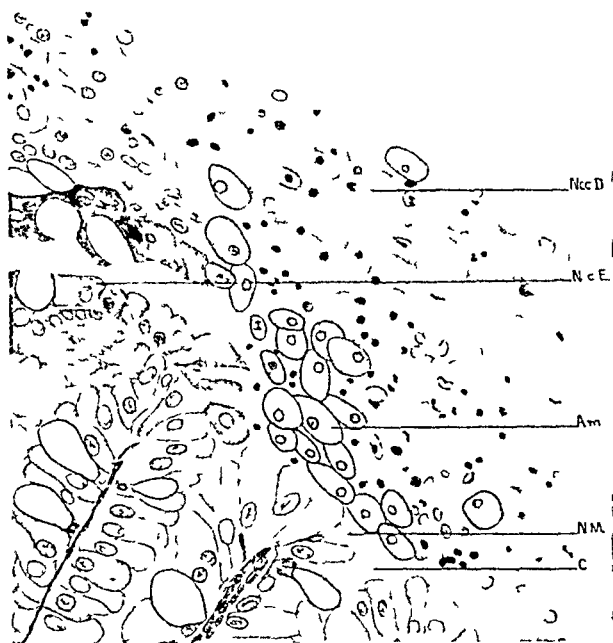


Fig 6—Camera lucida drawing of the outer margin of an ulcer in the colon of kitten 70,  $\times 350$

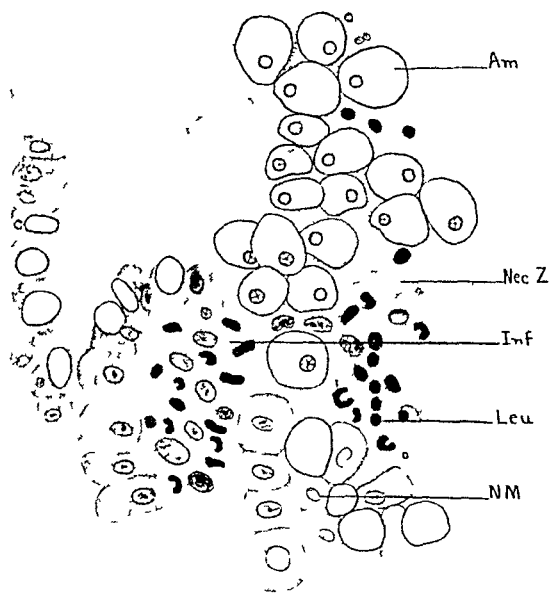


Fig 7—Camera lucida drawing of a portion of an ulcer in kitten 76,  $\times 350$   
 Abbreviations *Am*, amebas, *C*, crypt, *Inf*, zone of inflammation, *Leu*, leukocytes, *Nec Z*, zone of necrosis, *Nec E*, necrotic epithelium, *N M*, normal mucosa

Figure 9 was drawn from a section through a solitary lymph gland near the ileocecal valve of kitten 76 and illustrates what appeared to be an encounter between amebas and lymphocytes. A zone of necrosis separated the amebas from the normal cells within the gland.

A small section through a diphtheric membrane is represented in figure 10. The amebas had penetrated into the connective tissue between

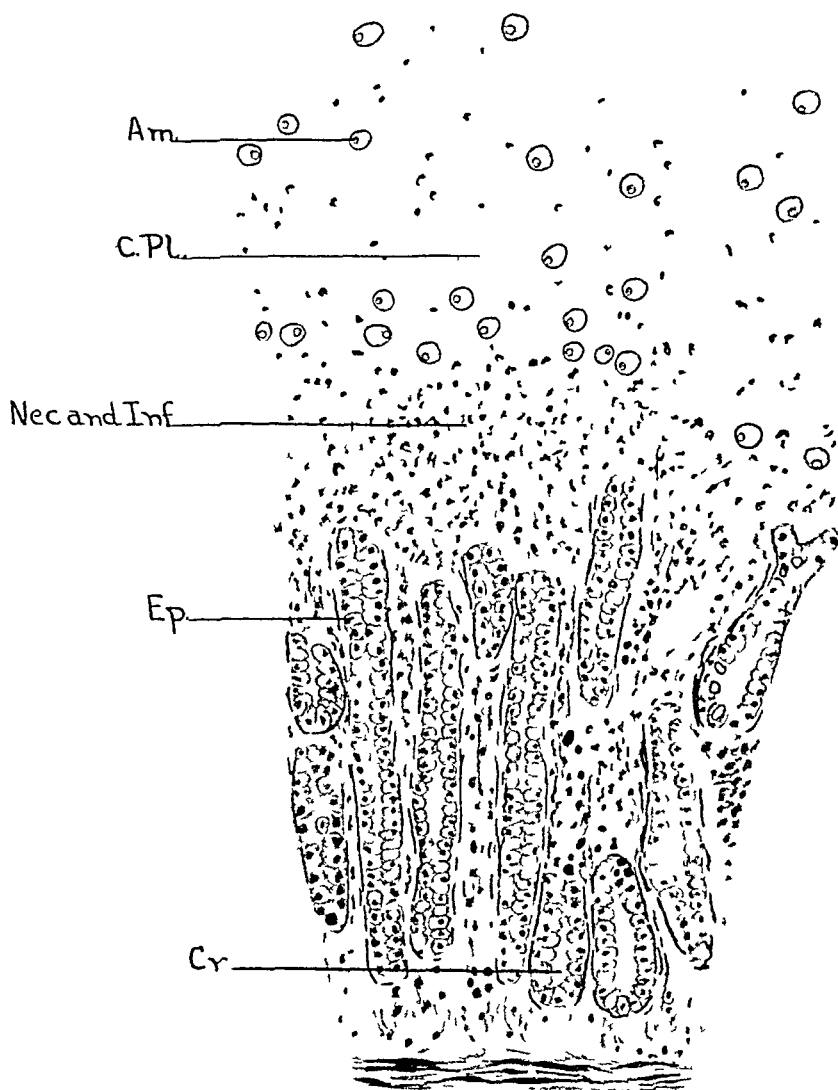


Fig 8—Camera lucida drawing of an ulcer of kitten 41,  $\times 175$ . Abbreviations: *Am*, amebas, *C Pl*, coagulated plasma, *Cr*, crypt, *Ep*, epithelium, *Nec and Inf*, zone of necrosis and inflammation.

the fundus of the glands and the muscularis mucosa and were seen in compact nests as though active multiplication had occurred there. The rest of the mucosa had almost completely disintegrated.

In all of the lesions studied, as well as in those figured and described, necrosis of tissue appeared to have commenced in the epithelium most

exposed to the fecal contents of the lumen. The lining epithelium of the crypts appeared normal in the early lesions, while cells not so situated appeared necrotic. A cytolytic toxin appeared to have been operative but conclusive evidence was not found that this toxin was excreted by the amebas.

It is not improbable, however, that the amebas may also have attacked the tissues by mechanical means. The work of Mast and Root,<sup>28</sup> who observed a free-living ameba cut a paramecium in two, indicated that ameboid organisms may engage in physical combat.

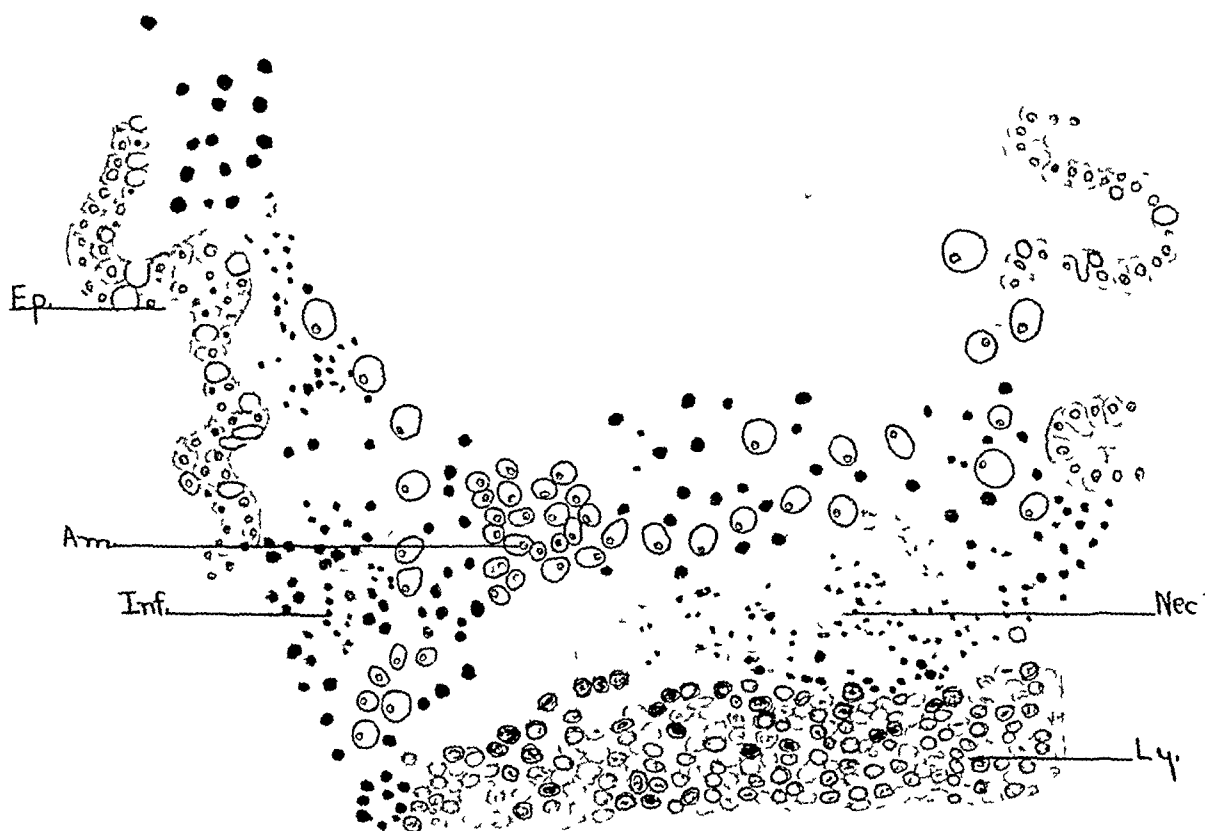


Fig 9—Camera lucida drawing of an amebic lesion in a solitary lymph gland of the colon of kitten 76 showing invasion of the gland by amebas.  $\times 175$

Abbreviations *Am*, amebas, *Ep*, epithelium, *Inf*, zone of inflammation, *Ly*, lymphocytes

#### GENERAL COMMENT

As stated previously, the chief objective of this work is to determine the method by which *Endameba histolytica* inflicts injury on the tissues of the colon. Some of the difficulties of such a study were anticipated

<sup>28</sup> Mast, S. O., and Root, F. M. Observations on Amoebae Feeding on Rotifers, Nematodes and Ciliates, and Their Bearing on the Surface Tension Theory, *J. Exper. Zool.* **9**: 301, 1908.

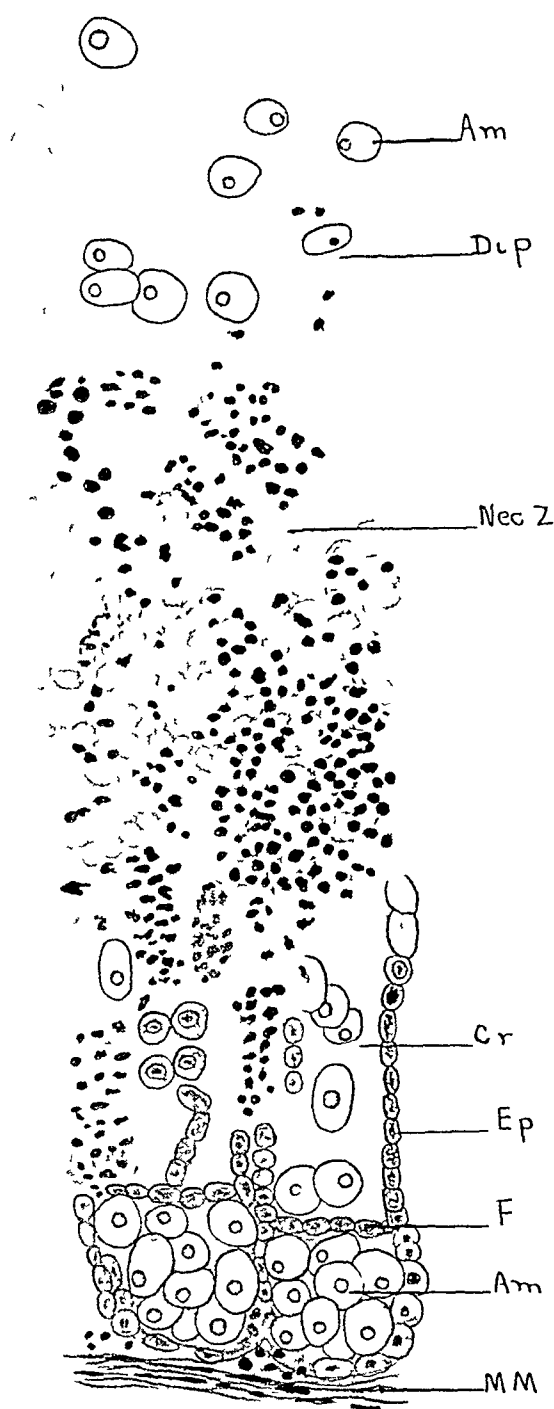


Fig 10—Camera lucida drawing through the mucosa of the colon of kitten 79 showing a diphtheric membrane,  $\times 350$

Abbreviations *Am* amebas, *Cr*, crypt, *Dip*, diphtheric membrane, *Ep*, remnants of epithelial cells, *F*, fundus of the gland, *MM*, muscularis mucosa

at the start, but as the work progressed many others appeared. The chief results thus far have been simplification of the problem by the surmounting of some of these difficulties. This will be made apparent by the discussion of the following questions: 1. Do the amebas multiply only within the lesions or is multiplication general throughout the entire fecal content of the infected bowel? 2. What are the steps in the process of the development of ulcers and are they the same whether in the areas first attacked or in other areas of the mucosa to which the infection spreads? 3. Does penetration of the tissue by the amebas continue after the death of the host, when the autopsy is not immediately performed? 4. What part in the production of lesions is played by the bacterial flora, that introduced with the ameba, as well as that already resident in the bowel?

Until the work of Boeck and Drbohlav,<sup>20</sup> it was generally held that multiplication of the amebas in the infected bowel occurred only within the tissues. But since the successful cultivation of this organism has been accomplished *in vitro* without the presence of tissue elements, several writers have suggested that multiplication may occur on the surface of the mucosa or even within the fecal content. From the viewpoint of pathogenesis, it is important to know where multiplication occurs, because it may be found that this factor influences the steps in the process of invasion of tissue and also the relation of these steps to the occurrence of symptoms. For example, if multiplication occurs only within the tissues, the following might be the sequence of events in those cases of infection which result from the ingestion of cysts. Only a few trophozoites would reach the colon, because not many cysts would be likely to be swallowed at one time. If conditions of survival required that the trophozoites attack the tissues at once, it is obvious that from one to several small lesions leading to ulcers would soon be produced. From these ulcers, the parasites would spread to attack other areas of the mucosa. When the lesions became sufficiently numerous and sufficiently severe, symptoms of dysentery would occur. According to this view, dysentery is a reaction of the host which follows ulceration due to injuries inflicted by the parasites.

On the other hand, if multiplication occurs also on the surface of the mucosa or in the fecal material within the lumen, the following might be the course of events. The trophozoites would multiply rapidly and, as is explained in detail in the foregoing paragraphs, soon would become sufficiently numerous to stimulate the secretory tissues of the bowel, producing diarrhea. Tissue invasion by the amebas would then occur and, as a result of the discharge of material from the ulcers, the symptoms would become those of dysentery.

I believe that in the kittens studied multiplication of the amebas occurred within the lumen in the fecal material independent of the



ulcers As evidence, I cite the following observations 1 As stated in the review of the literature, *E histolytica* thrives when cultivated in vitro even to the completion of its life cycle, therefore, access to living tissue is not obligatory 2 Ingestion of starch causes it to grow and divide much more rapidly than it does when this food is not available Therefore, the nutritive conditions for optimal growth do not necessarily involve living tissue 3 Within the lesions the reaction of the host appeared to kill the amebas or at least to injure them so that multiplication was retarded (figs 3 and 5) 4 Diarrhea appeared in all the kittens infected by rectal injection as soon as the fecal diagnosis was positive, that is, at the end of the prepatent period When kittens were killed at this time and examined microscopically, there did not appear to be enough ulcers to serve as a multiplication ground for the enormous numbers of trophozoites occurring in the feces 5 In the sections, there was evidence of multiplication of the amebas within the lesions (fig 10), but there was not any indication that necrotic material containing amebas had been discharged into the lumen from any of these early lesions Since the feces were usually teeming with the organisms, it did not appear probable that they could all have been derived from material discharged from the ulcers 6 Kittens 30 and 35 were affected for ten and thirteen days, respectively, with amebiasis, and yet no lesions containing amebas could be found in sections of these colons On the other hand, the following facts indicate the need of caution before committing oneself definitely concerning the multiplication of these parasites The kittens referred to were infected by rectal injection and not by the natural means of ingesting cysts The five cubic centimeters of fluid usually injected were enough to fill half of the colon of such young kittens and no doubt contained many more amebas than would reach the colon at one time if the animal ingested the cysts Furthermore, fecal diagnosis was negative in kittens 33, 74 and 79 of table 3, and yet the colons of the first two were found to contain amebas at autopsy, while the latter must have been infected because of the diphtheric membrane which developed in twenty-six hours following laparotomy (table 2) These observations satisfied the requirements for the view that multiplication occurs only within the lesions Then, again, diarrhea and sometimes dysentery occurred in some of those kittens that were not infected with amebas This fact indicated that other agencies may have operated also in the kittens that were found infected Hence the need of further research on this question Should it be definitely established that the amebas multiply within the lumen and that diarrhea precedes ulceration of the colon, a strong case will have been built up for the theory that the amebas excite a toxic substance It appears improbable that without such excretion their mere presence in the bowel would excite the glands to an extent necessary to cause this symptom

The second question stated in the foregoing part of this article concerns the steps in the process of the production of ulcers. Wenyon<sup>15</sup> described these steps in the cat as follows

In sections of the ulcerated gut it is easy to study the invasive process. The amoebae make their way to the bottom of the tubular gland in the large intestine. There they multiply and by pressure of their number or by the exertions of their pseudopodia and probably through some toxic substance excreted by them, the lining cells are weakened and separated and the amoebae pass into the connective tissue beneath. The epithelial cells commence to degenerate and the earliest stage of ulceration is reached. Bacteria are thus admitted and the destruction becomes more rapid while the amoebae push on to deeper layers and give rise to the characteristic undermined ulcers.

The data on which this author's statements were based had been obtained from observation of a series of kittens, of which six became infected with amebic dysentery. Three died during the night, and three were killed. Figures were not given to illustrate the successive steps in the process described. Wenyon<sup>21</sup> expressed the same opinion concerning human amebiasis, and stated further that human colons at autopsy "show every stage in the production of ulcers from the smallest yellow nodules to the large undermined ulcers." According to this view, the invasive process is the same whether studied in human beings or in kittens. As Wenyon speaks of undermined ulcers in the kittens which he studied, the lesions were much farther advanced than those of the present series. Careful drawings and descriptions presented by myself in the foregoing pages are evidence that in the kitten the steps in the invasive process are at least not always as described by Wenyon. A gland was found occasionally to be occluded in the colons of kittens 33, 83, 88 and 89, infected by rectal injection. Such glands appeared greatly distended by the continued secretion of mucus, and the epithelial cells appeared to have been flattened by the pressure thus produced. Some of these enlarged glands contained leukocytes, but amebas could not be found in any of them. But the glands were found almost always to be opened out toward the lumen rather than occluded, and the secretion of mucus appeared as the most marked characteristic of the reaction of the host. This altered condition of the crypts and the outflow of mucus may have prevented the migration of the amebas into these glands, particularly after dysentery had appeared. Necrosis of tissue always commenced in the epithelium outside the crypts. The inflammatory reaction became manifest in the connective tissue between the crypts, and there was evidence of an outflow of plasma and an outwandering of leukocytes. Necrosis continued until the entire mucosa became involved in the ulcer.

Concerning question 3, I observed a phenomenon which is here termed postmortem penetration, that is, continued invasion of the tissues

of the host, after the death of the latter, by the amebas. Kitten 23 of table 2 died during the night as a result of a poorly conducted operation. That it had been dead some time when autopsy was performed twenty-four hours after the operation was indicated by the temperature of the body, the condition of the colon and other organs and by the fact that though there were many active amebas in several hemorrhagic ulcers, none were present in the feces within the colon. The ulcers were about 2 mm in diameter—as large as many of those found regularly in kittens killed several weeks after the close of the prepatent period following rectal injection. It appears remarkable that such large ulcers should have been produced solely by the amebas in so short a time. They were not present, however, at the time of the operation or they would have been observed, since at autopsy they were plainly visible in the wall of the colon before it was opened. Therefore it appears that, in this case, the amebas were able to penetrate the tissue after the death of the host much more rapidly than while the latter was living. Similar ulcers were seen in the colon of kitten 62 of table 2, but this animal died during the third twenty-four hour period following the operation. Scott,<sup>29</sup> working with *Balantidium* in the guinea-pig, noted that this ciliated protozoan may penetrate the mucosa of the cecum after the death of the host. She did not furnish evidence that such penetration occurs during the life of the latter.

As is well known, autopsies on human beings are seldom conducted immediately after death, frequently there is a lapse of from twenty-four to seventy-two hours. Councilman and Lafleur<sup>23</sup> (1891) and Wenyon<sup>21</sup> (1925) reported that amebas were usually found living in the tissues at the end of such periods. Dobell and Laidlaw<sup>17</sup> showed that *E. histolytica* might remain living in vitro at room temperature for three days. But cooling occurs more slowly in human beings than in kittens, so that in the former there is a considerable period during which the amebas may work at a temperature near the optimum. It is not improbable that under such conditions, without having to combat the resistance of the host, the parasites may penetrate rapidly.

It seems clear from the foregoing discussion that the procedure I adopted and the precautions I took were necessary. Briefly summarized, these were (1) to study the symptoms of infected kittens and to consider them in connection with the lesions found at autopsy, (2) to use several methods of infecting kittens and to compare the kittens with each other and with controls, (3) to kill the kittens in the earliest stages of infection as well as in later stages and thus secure a series as complete as possible from the earliest lesions to well developed ulcers, (4) to

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<sup>29</sup> Scott M. J. Studies on the *Balantidium* from the Guinea Pig, J. Morphol. & Physiol. 44: 417, 1927.

study the lesions while the colon was still living and also in the freshly fixed colon as well as in the sections, (5) to kill tissues for sectioning with fixing fluids, but if this were impossible, to fix them as quickly after death as possible, (6) to study the mucosa of the entire colon, that already invaded by the amebas as well as that not so invaded. It will be granted that whether or not the steps in the invasive process are the same in human beings as in kittens, the weapons of attack of the amebas are always the same. I hold that pathogenesis may be much more satisfactorily studied in the kitten, because the experimental method may be applied. Furthermore, I believe that a clearer picture may be obtained from kittens killed in the early stages of amebiasis than from sections which have advanced to the stage of undermined ulcers with overhanging margins.

Question 4 concerns the complications caused by bacteria, which are always present with the amebas in the cultures and in the colon to which they are introduced. Thus far, little attention has been paid to a study of this factor, though its importance is realized. It is well known that the healthy bowel is not affected by the bacteria commonly living within the feces. It has been amply demonstrated by earlier workers as well as in this work that the bacteria commonly found associated with the amebas do not produce lesions when introduced without amebas into the colon. In this work, such lesions did not occur when amebas were introduced with the bacteria unless the protozoan parasites established themselves. But bacteria do invade all wounds that are accessible to them, and an inflammatory reaction occurs whenever a wounded surface is left exposed to their attack. Cytolytic products are produced, and necrosis of the tissue occurs. In the lesions studied and illustrated in this article, an inflammatory reaction was always manifest. According to most authorities on the pathology of amebiasis, inflammation is not one of the reactions of the body resulting from the form of injury inflicted by amebas. The best evidence for this belief is that amebic lesions of the liver, which do not contain bacteria, are not true abscesses, that is, the inflammatory reaction is absent.

It is obviously impossible to exclude bacteria from the colon of the kitten, and no one has thus far demonstrated that amebas free from bacteria can be grown in culture. Since the objective of this work is to determine what weapons the amebas use, the problem is seriously complicated by the bacteria. It has been impossible up to the present time to discriminate clearly between the results of bacterial activity and the results of amebic activity. Unless some method of doing so can be developed, it may be necessary to devise experiments involving tissue culture from which they can be excluded.

## SUMMARY

1 This investigation was undertaken with the object of obtaining information on the methods employed by *Endameba histolytica* in its attacks on the tissues of the colon in kittens

2 The kitten was chosen as the experimental animal because of its well known susceptibility to amebiasis

3 The amebas were grown in culture in Boeck and Drbohlav's egg slant serum medium, and for the earlier experiments this medium was enriched by rice starch

4 Two methods of infecting kittens were used that of an injection of the material through the wall of the ligated colon following laparotomy, and that of rectal injection without a subsequent closing of the anus

5 Eighty-four kittens were used and, from fifty-eight of these, data of value to this problem were obtained Prepared slides of sections through amebic lesions were studied from fourteen kittens infected after laparotomy and from eight infected by rectal injection

6 Amebic lesions could not be found in kittens that were proved infected after laparotomy when killed in less than forty hours after the operation, but lesions of great severity frequently were found after ninety hours, involving complete destruction of the mucosa and the investment of the colon by a diphtheric membrane

7 When the amebas did not succeed in establishing themselves after laparotomy, the mucosa was normal up to ninety hours

8 With the aid of the binocular microscope, minute lesions could be detected in a freshly fixed colon Entire colons were frequently sectioned in an effort to find all the lesions

9 The first ulcers that were detectable after laparotomy usually occurred near the ileocecal valve, and the lesions were always most severe in this area after rectal injection

10 In kittens killed from four to thirty-four days following the injection of trophozoites through the anus, there were often well developed ulcers and also minute lesions, but the submucosa appeared not to be invaded in any case

11 Infection followed much more frequently when feces from an infected kitten were injected than when amebas in culture were used.

12 The earliest observed symptom of intestinal amebiasis was diarrhea, which occurred at the close of the prepatent period (from two to five days) Evidences of anatomic alterations in the colon following diarrhea were found to consist in enlarged glands and pronounced goblet cells

13 Ulcers in the colon were studied under the binocular microscope in Locke's solution while the tissue was still living. They appeared as hyperemic areas. Tissue was teased from these lesions and was found, under higher magnification, to contain living active amebas, which were suggestive of active tissue invaders.

14 In one colon, the invasion by the amebas of a solitary lymph gland was noted and figured.

15 The evidence of the lesions studied in this work does not support the view of several authorities that the initial attack of the amebas on the mucosa commences within the crypts, leading to the occlusion of the latter and the development of abscesses.

16 In all the material studied from kittens infected both after laparotomy and by rectal injection, the amebas appear to have begun the attack on the mucosa, that is, outside of the crypts. The ulcers appeared to be developed therefore by necrosis beginning at the surface, and not by the discharge into the lumen of necrotic material from abscesses.

17 The attack of the amebas appeared to have provoked a reaction of the host comprising hypersecretion of mucus and hyperemia. Other evidences of inflammation were also manifest, but the part played by bacteria in this reaction could not be ascertained.

18 There was evidence that the amebas were injured by the reaction of the host.

19 Although this investigation is still in progress, these data are published at this time because evidence heretofore presented has not included descriptions and figures of early lesions. Furthermore, the data support the view stated heretofore that the method of producing ulcers is different from that usually described.

#### CONCLUSIONS

In this investigation thus far, the nature of the attack of *Endameba histolytica* on the colon has not been definitely determined. This is due mainly to complicating factors which confuse the picture. But the results of the experiments suggest that the following events occur. The amebas multiply within the lumen of the colon and produce a toxin which causes the host to react by the hypersecretion of mucus, and diarrhea results. In various areas where conditions for the multiplication of the parasites have been most favorable, they attack the epithelial cells of the mucosa. The host responds by a more rapid secretion of mucus and plasma. These fluids envelop and apparently injure some of the amebas. But continued attack by amebas leads to an injury sufficient to cause bleeding. The amebas profit by this food and ingest the red blood cells. They continue to invade the tissue until an ulcer is formed,

extending to the muscularis mucosa. Beyond this point the infection was not followed in my material. The hypersecretion of the glands, the hyperemia and the rapid necrosis of tissue indicate the excitation by the amebas of a cytolytic toxin. In many of the lesions, the amebas were not in immediate contact with the cells but separated by a zone of necrosis. This also suggests their ability to inflict injury by means of toxins. Another method of attack may consist in the actual destruction of cells by physical means, as has been reported in the case of free-living amebas. This might result in injuries to the tissues that bring about bleeding. The general occurrence of bacteria in the lesions complicates the problem, because they may cause much of the necrosis that one could otherwise definitely attribute to the amebas.

# METAPLASIA OF BASAL CELLS IN THE DUCTS OF THE PANCREAS ITS CONSEQUENCES \*

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## THE PROBLEM OF METAPLASIA OF BASAL CELLS

When Krompecher<sup>1</sup> in his early investigations of tumors of the skin first recognized the fact that the "rodent ulcer" was clinically as well as histologically a special type of tumor, he created the term, "basal cell carcinoma." His work showed that these tumors of the skin grow slowly, metastasize rarely and then only late, and that they do not tend to recur after excision, also, that the cells which compose these tumors resemble those occurring in the malpighian layer of stratified epithelium of the skin, form solid cell groups and arrange themselves in a plexiform manner.

Further investigations by Krompecher<sup>2</sup> and others demonstrated that the basal cells which are found between the cylindrical cells and the membrana propria of glandular organs can proliferate in a similar manner and give rise to basal cell carcinoma. Krompecher demonstrated such alterations in the mucous membrane of the nose, bronchi, uterus, prostate, breast, larynx, intestine and parotid gland. He drew attention to the fact that basal cell tumors in internal organs differ from basal cell tumors of the skin in that the former behave more like malignant tumors.

Krompecher believed that basal cell carcinoma could result from the proliferation of basal cells. He regarded the latter as a preliminary to cancer. He thought that the toxins of different bacteria act as irritants on the basal cells of different mucous membranes and lead to their proliferation.

In many instances experimental investigations have confirmed the morphologic observations which Krompecher recorded. For example, it has been shown that the benign epithelial proliferation which occurs at an early stage in the experimental production of tar cancer, can later give rise to a really malignant tumor. In this way, a potential difference between a relatively benign carcinoma, such as "rodent ulcer," and a really malignant basal cell carcinoma was disproved.

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<sup>1</sup> From the Pathological Anatomical Institute of the Hungarian Royal Francis Joseph University, Szeged.

1 Krompecher. *Der Basalzellenkrebs*, Jena, Gustav Fischer, 1903.

2 Krompecher. *Beitr z path Anat u z allg Path* **44** 88, 1908, **65** 79, 1919, **70** 489, 1922, **72** 163, 1924, **76** 113, 1927, *Ztschr f Geburtsh Gynak* **81** 299, 1919, *Arch f Laryngol & Rhinol* **31** 443, 1918.



Brusis<sup>3</sup> ligated the ducts of the submaxillary glands in rabbits and after fourteen weeks demonstrated proliferative changes in the ducts. Ribbert<sup>4</sup> observed in the parotid glands of rabbits, similarly treated, changes even more striking and bearing a close resemblance to carcinoma. Lowenstein<sup>5</sup> reported basal cell changes in the duct of the parotid gland in a case of Mikulicz's disease, in tuberculosis and in status lymphaticus. Krompecher regarded the tumors composed of mixed types of cells in the parotid gland, previously known as myxo-endothelioma, as myxobasaloma.

Kawamura<sup>6</sup> produced metaplasia of the bronchial epithelium experimentally by irritants. Goldzieher<sup>7</sup> found basal cell changes in the larger bronchi in a case of diphtheria, while Teutschlander<sup>8</sup> noted similar changes in the lungs of rats which had died from bronchopneumonia and in the lungs of a child who had died from measles. Askanazy<sup>9</sup> could demonstrate metaplasia of basal cells in the lower respiratory passages in thirty-eight of ninety cases of epidemic influenza, and he also observed such changes in two cases of typical pneumonia.

Szabo<sup>10</sup> noted metaplasia of basal cells in the prostate, and Wolf<sup>11</sup> in the ductus deferens following gonorrheal epididymitis.

Krompecher regarded the so-called carcinoids in the intestines as tumors which had resulted from metaplasia of the basal cells.

Krompecher's statement that a proliferation of basal cells in glandular organs could be a preliminary to cancer has been verified by the occurrence of basal cell carcinoma in those organs in which a proliferation of basal cells was also found. Thus von Meyenburg<sup>12</sup> reported a basal cell tumor of the trachea, Siegmund<sup>13</sup> three similar tumors of the lung and B. Meyer,<sup>14</sup> among others, a basal cell carcinoma of the right main bronchus, which developed in a patient 53 years of age, following influenza. Wutsuji<sup>15</sup> has observed such tumors in the gall-bladder.

3 Brusis. Dissertation, Marburg, 1903, cited by Krompecher. Beitr. z. path. Anat. u. z. allg. Path. **70** 499, 1922.

4 Ribbert. Verhandl. d. deutsch. path. Gesellsch. **6** 133, 1904.

5 Lowenstein. Frankfurt Ztschr. f. Path. **4** 187, 1910.

6 Kawamura. Virchows Arch. f. path. Anat. **203** 420, 1911, Ijishinbun, Japan, 1908, p. 753.

7 Goldzieher. Centralbl. f. allg. Path. u. path. Anat. **29** 506, 1918.

8 Teutschlander. Centralbl. f. allg. Path. u. path. Anat. **30** 433, 1919.

9 Askanazy. Cor.-Bl. f. Schweiz. Aerzte **49** 75, 1919, cited, Centralbl. f. allg. Path. u. path. Anat. **30** 443, 1919.

10 Szabo. Magyar Orvosi Arch. **26** 248, 1925.

11 Wolf. Virchows Arch. f. path. Anat. **228** 227, 1920.

12 von Meyenburg. Centralbl. f. allg. Path. u. path. Anat. **20** 130 and 578, 1919.

13 Siegmund. Virchows Arch. f. path. Anat. **236** 191, 1922.

14 Meyer. Frankfurt Ztschr. f. Path. **271** 517, 1922.

15 Wutsuji, cited by Krompecher. Beitr. z. path. Anat. u. z. allg. Path. **76**: 113, 1927.

## REVIEW OF THE LITERATURE ON THE PROLIFERATION OF BASAL CELLS IN THE DUCTS OF THE PANCREAS

Kawamura<sup>6</sup> found the lining epithelium of the duct of Wirsung and its middle size branches changed from cylindrical to multilayer epithelium in a patient 43 years old, who suffered from distomum spathulatum of the pancreas. Nunokawa<sup>16</sup> and Nakamura<sup>17</sup> recorded similar observations. Kawamura remarked that, although distomum spathulatum occurs simultaneously in the biliary ducts of the liver and in the ducts of the pancreas, he found alterations which he regarded as due to metaplasia of the basal cells only in the ducts of the pancreas. In his case as well as in that reported by Nunokawa, the pancreatic duct showed inflammatory changes and the pancreas a chronic pancreatitis.

Kolliker<sup>18</sup> stated that the epithelium of the larger pancreatic ducts is of the cylindrical type, and that the height of the cells in these ducts is from 13 to 18 microns or, in the smaller ducts, from 5 to 7 microns.

The transformation of the cylindrical epithelium of the pancreatic ducts to multilayer epithelium, in three cases, was reported by Oberling.<sup>19</sup> In every instance the patient was over 50 years old, and the alterations were associated with interstitial pancreatitis.

The largest number of cases of metaplasia of basal cells in the pancreas previously reported are those recorded by Priesel.<sup>20</sup> He examined 140 cases and observed metaplasia of basal cells in thirteen instances. From his work it is evident that metaplasia of basal cells in the ducts of the pancreas cannot be regarded as of rare occurrence, but is apparently present in somewhat less than 10 per cent of cases. Priesel stated that metaplasia of basal cells in the pancreas occurs in elderly people, because ten of his cases were in persons over 60 years of age.

In his series the pancreas in five instances was normal. In one case, the organ showed a carcinoma. This tumor, however, did not arise from proliferating epithelium of a duct. It was of the glandular type. In two cases the pancreas contained a cystadenoma. In three, lipomatosis was noted, twice with formation of cysts. The cysts in his case 12, were not related to metaplasia of basal cells, although in another case a connection between the proliferation of basal cells and the formation of cysts was accepted. The remaining two cases were diabetes. Priesel regarded the alteration in the ducts of the pancreas as prosoplasia.

Scholtz<sup>21</sup> reported one case of metaplasia of basal cells in the ducts of the pancreas. She stated that the cause of this alteration was

16 Nunokawa, cited by Kawamura (footnote 6)

17 Nakamura. *Med Wchnschr zu Kyoto, Japan* 5 1, 1908

18 Kolliker, cited by Kawamura. *Virchows Arch f path Anat* 203 420, 1911

19 Oberling. *Bull de l'Assoc franç p l'étude du cancer*, 1921, p 155

20 Priesel. *Frankfurt Ztschr f Path* 26 453, 1922

21 Scholtz. *Virchows Arch f path Anat* 247 467, 1923

unknown Abdrachmanoff<sup>22</sup> and Herxheimer<sup>23</sup> reported similar cases. Weichselbaum,<sup>24</sup> in his studies on the regeneration of the islands of Langerhans, noted proliferative changes in the ducts of the pancreas, while Kyrle<sup>25</sup> and Weichselbaum observed such changes in the duct of Wirsung in animals shortly after the ducts had been ligated.

Israel<sup>26</sup> described a cancrroid in the pancreas of a man aged 50, and Lewisohn<sup>27</sup> a similar condition in a man aged 67, in which the pancreatic duct beyond the point of obstruction was markedly dilated and the pancreatic tissue necrotic. Kawamura regarded cancrroids of the pancreas, gallbladder and lungs as being of similar origin. Herxheimer<sup>28</sup> reported the combination of an adenocarcinoma and basal cell carcinoma of the pancreas. Cysts were noted in the tail of the pancreas. Askanazy<sup>29</sup> recorded two cases of basal cell carcinoma of the pancreas.

It is therefore surprising that Walz<sup>30</sup> should have stated that to the year 1926 basal cell tumor of the pancreas had not been reported.

#### AUTHORS' OBSERVATIONS ON METAPLASIA OF BASAL CELLS IN THE DUCTS OF THE PANCREAS

In order to determine the relative frequency of metaplasia of basal cells in the ducts of the pancreas, we examined a series of 160 pancreases. Fresh specimens were obtained from the Pathological Department of the Metropolitan Saint Stephen's Hospital, Budapest. At least five or six sections from the head, body and tail were examined, and usually from eight to ten or more.

Table 1 shows that a proliferation of basal cells had occurred in fourteen of the pancreases examined, which means in 8.75 per cent.

Our chief interest was directed to the pathologic consequences of metaplasia of basal cells in the pancreas, and to its cause.

*General Observations*—The replacement of the cylindrical epithelium of the pancreatic ducts by basal cells was found especially in the middle size and smaller ducts. Here the basal cells were often seen to have proliferated in a circumscribed manner, forming little buds or pillows. These buds were usually composed of several layers of basal cells and

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22 Abdrachmanoff. These de Geneve. Contribution a l'anatomie pathologique du pancreas diabetique, 1912.

23 Herxheimer. Gewebsmisbildungen in Schwalbes Handbuch, Jena, 1913.

24 Weichselbaum. Sitzungsber d Wiener Akad d Wissenschaft, 1908, pt 3, p 117, 1910, pt 3, p 119.

25 Kyrle. Arch f micr Anat **72** 141, 1908.

26 Israel. Berl klin Wchnschr **33** 45, 1896.

27 Lewisohn. Ztschr f Krebsforsch **3** 528, 1905.

28 Herxheimer. Beitr z path Anat u z allg Path **41** 348, 1907.

29 Askanazy, cited by Priesel. Frankfurt Ztschr f Path **26** 513, 1922.

30 Walz. Centralbl f allg Path u path Anat **37** 748, 1926.

in some instances were partly covered by cylindrical cells. They rather frequently projected into the lumen of a duct, which was thus narrowed. In serial sections, it could be noted that these buds were occasionally small and consisted of but few cells.

There were occasions when the metaplasia of basal cells involved the whole circumference of the duct. Sometimes the terminal portions of the ducts could be seen filled by groups of cells arranged in a solid manner. One not infrequently got the impression that the proliferation of

TABLE 1—*Conditions Associated with Metaplasia of Basal Cells in the Pancreas*

Case	Age	Sex	Disease	Accompaniment in Pancreas	Jaundice	Gall stones	Diabetes
1	24	M	Cardiac	Dilatation of ducts, enlargement of the islands of Langerhans, necrotic areas	+	0	0
2	19	F	Endocarditis	Small necrotic areas	0	0	0
3	70	F	Cholecystitis (stones) died after cholecystectomy	Lipomatosis	+	+	0
4	75	F	Carcinoma of the gallbladder	Lipomatosis, cysts, necrotic areas	+	+	0
5	56	F	Pulmonary embolus after colporrhaphy	Lipomatosis, cysts, adenoma of an island of Langerhans	0	0	0
6	27	M	Chronic endocarditis	Necrotic areas	+	0	0
7	46	F	Acute yellow atrophy of the liver	Necrotic areas	+	0	0
8	67	M	Carcinoma of the choledochus	Dilated ducts, increased connective tissue, slight lipomatosis	+	0	0
9	54	F	Cardiac insufficiency	Lipomatosis, enlarged islands of Langerhans	0	0	0
10	30	M	Periarteritis nodosa	Slight lipomatosis, dilatation of some ducts	0	0	0
11	19	M	Lymphogranulomatosis	Diffuse dilatation of ducts	+	0	0
12	47	F	Cholecystitis, cholelithiasis	Slight lipomatosis	+	+	0
13	62	M	Myocarditis	Lipomatosis, formation of cysts	+	+	0
14	36	F	Puerperal sepsis		+	+	0

basal cells could bring about the formation of smaller or larger solid cell groups.

The metaplasia of basal cells was interpolated with the normal cylindrical epithelium, and could be observed in the various parts of the duct system. Even when the proliferation of basal cells was widespread, hornification was seldom observed. Masses of a horny substance arranged in concentric layers could, on a few occasions, be seen within the ducts. The proliferation of basal cells occurred most frequently in the tail of the pancreas.

The consequences of the metaplasia of basal cells in the ducts of the pancreas were observed to be, in reality, consequences of the narrowing or partial obliteration of the lumen of ducts.

*Effects of Metaplasia of Basal Cells in the Ducts of the Pancreas on the Pancreas 1 Flattening of the Cells of the Acini*—It is well known that the lumen of a pancreatic acinus, or end chamber, is normally hardly visible, because it is lined by cells of a high type. Dilatation of the lumen of an end chamber can be brought about by any factor which causes narrowing of a pancreatic duct and mechanical retention of pancreatic secretion. We believe that a metaplasia of basal cells in the duct of the pancreas can be responsible for such a change.

It depends on the location and extent of the metaplasia of basal cells whether the dilatation of pancreatic acini is general or circumscribed.

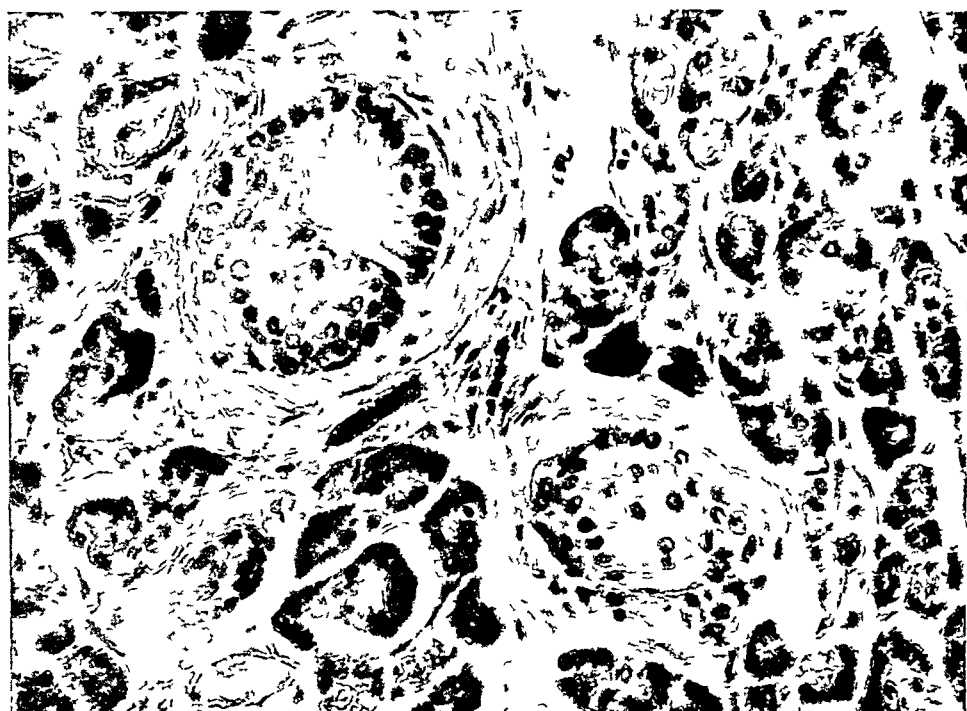


Fig 1 (case 1)—High power magnification, showing metaplasia of basal cells in two small pancreatic ducts. The lumen of both ducts is greatly narrowed, but the metaplastic changes in each case occupy only a part of the duct circumference.

The dilatation of end chambers is such a common consequence of the metaplasia of basal cells that we used this phenomenon as a satisfactory indicator in collection of our cases. Thus, wherever we noted dilatation of end chambers we would always look for a metaplasia of basal cells in the corresponding ducts.

The cells which line the acinus in such cases are only as high as their nuclei, while the dilated lumen of the acinus can be filled by coagulated secretion. This flattening of the epithelium may in some instances be so uniform that were it not for the presence of the islands of Langerhans one could easily mistake such a section for one of thyroid tissue.

The extent to which the acini are dilated is variable and is naturally dependent on the degree to which the ducts have been narrowed

2 *Formation of Cysts*—In three of our cases a formation of cysts was found in the pancreas. The cysts varied in size from that of a millet seed to that of a pea. They were lined by cylindrical epithelium and in some places also by multilayer epithelium corresponding with the metaplasia of basal cells. Where cylindrical and stratified epithelium joined, the cylindrical epithelium sometimes covered the stratified epithelium in the same way as it does in erosions of the cervix uteri.

Priesel followed the relationship of the metaplasia of basal cells to the formation of cysts in the pancreas. In serial sections, he was able to

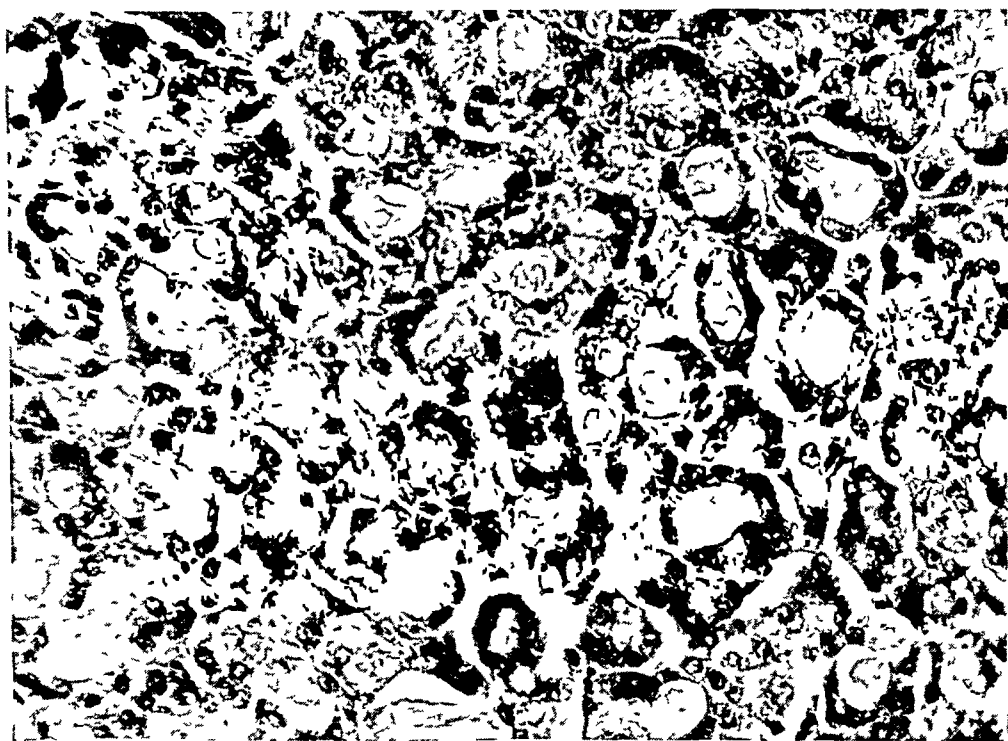


Fig 2 (case 11) —Dilatation of end chambers due to the metaplasia of basal cells in small pancreatic ducts. The acini are filled by a homogeneous secretion, and the cells which line them are flattened.

prove that cysts are formed behind the metaplasia of basal cells in the ducts. We have confirmed these observations. We consider that the cysts are due to a dilatation of that portion of the secretory system which is behind the narrowing caused by the proliferation of basal cells. It is probable that proliferating basal cells, penetrating here from the proximal part of the ducts, can later on line these cysts.

Dilatation of the end chambers as a consequence of the metaplasia of basal cells in the ducts is a much more common occurrence than the formation of cysts. The dilatation of the end chambers on the one

hand or the formation of grossly visible cysts on the other likely depends on the localization of the metaplasia of the basal cells. In the latter case, the larger branches are evidently the seat of the metaplasia of basal cells.

3 *Focal Necrosis*—Small necrotic areas the size of a poppy seed or larger were found in the pancreas in five of our cases (nos. 1, 2, 4, 6, 7). In three of these cases, endocarditis, in one, carcinoma of the gall bladder, and in the remaining one acute yellow atrophy of the liver were associated observations. Jaundice was present at necropsy in four of the cases.

Only those small necrotic areas around which some inflammatory reaction on the part of the surrounding tissue, but more especially leukocytic infiltration, could be noted were regarded as having occurred *intra vitam*. In another article<sup>31</sup> we pointed out that in cases in which jaundice due to alterations of the papilla of Vater occurs, retention of pancreatic secretion can also take place. We have already mentioned that in four of five cases of basal cell metaplasia which were complicated by focal necrosis jaundice was present. An ascending infection in the pancreas was therefore possible in these cases. The relationship between focal necrotic areas and the metaplasia of basal cells in the ducts could be twofold. The one might be that the metaplasia of basal cells plays a direct part in the production of focal necrosis, the other that both the focal necrosis and the metaplasia of basal cells are consequences of stasis or of ascending inflammatory processes in the pancreas. We shall see that not all cases of metaplasia of basal cells are to be interpreted as being due to stasis or to an ascending infection. It is probable that a metaplasia of basal cells acts rather as a factor predisposing the pancreas to focal necrosis, that when the retention of pancreatic secretion occurs, the consequences of such retention are more severe in those areas in which the metaplasia of the basal cells occurs and in which it has already narrowed the duct system.

4 *Lipomatosis*—Another possible consequence of the metaplasia of basal cells in the pancreas is lipomatosis. We observed such changes in the pancreas in eight of the cases which we have reported. It was Priesel who first described the combination of lipomatosis, cyst formation and basal cell metaplasia in the pancreas. We have observed such a combination in our material on three occasions.

We believe that lipomatosis of the pancreas in the majority of cases results from the breaking down of pancreatic tissue, which is replaced by fat. Exact proof of the origin of pancreatic lipomatosis can be established only by quantitative chemical determinations and by the comparison of the fat content of the normal pancreas and of the pancreas

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31 Baló and Ballon. Surg. Gynec. Obst., to be published.

in which lipomatosis has occurred One of us made these determinations and found that lipomatosis of the pancreas is mostly due to replacement of broken down glandular tissue by fat

The breaking down of glandular tissue can take place in different ways Focal necrotic areas were noted in five of our cases of metaplasia of basal cells Such areas can later on be replaced by fat Focal necrosis in the pancreas can recur, just as stasis of pancreatic secretion and an ascending inflammatory process can take place, repeatedly

The sudden breaking down of pancreatic tissue takes place in the form of focal necrosis The chronic retention of pancreatic juice is followed by a flattening of the cells lining the acini, a gradual disappearance of glandular tissue and by an increase in fat in the pancreas This can be compared with the lipomatosis of the pancreas that results in animals following a ligation of ducts

We believe that metaplasia of basal cells, by causing the narrowing of the lumen of ducts, can bring about alterations in the pancreas similar to those noted after experimental ligation of ducts

5 *Hypertrophy of the Islands of Langerhans*—The enlargement of the islands of Langerhans has been described by several workers Cecil,<sup>32</sup> MacCallum,<sup>33</sup> Herxheimer<sup>34</sup> and many others long ago demonstrated the presence of degenerated and hypertrophied islands of Langerhans in the pancreas in cases of diabetes That the islands of Langerhans enlarge as a result of obstruction or ligation of the pancreatic ducts is well known Starvation may also cause them to enlarge

Ssobolew<sup>35</sup> reported a case of diabetes in which an enlarged island of Langerhans had a diameter of 1.5 mm He made mention of a "struma of the islands of Langerhans"

Since metaplasia of basal cells can also obstruct the lumen of ducts the question naturally arises as to what relationship metaplasia of basal cells bears to hypertrophy of the islands of Langerhans For in several of our cases we found enlarged islands of Langerhans

It has been proved that a regeneration of islands of Langerhans can take place from smaller ducts There is thus the possibility that the buds which are formed in the early stages of a metaplasia of basal cells resemble a regeneration of the islands of Langerhans

When the whole circumference of a duct is altered to epithelium of the multilayer type then this condition cannot be confused any more with a regeneration of the islands of Langerhans

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32 Cecil J Exper Med **11** 266, 1909

33 MacCallum Am J Med Sc **43** 432, 1907

34 Herxheimer Virchows Arch f path Anat **183** 228, 1906

35 Ssobolew Virchows Arch f path Anat **177** 123, 1904



It seems rather unlikely that the buds which we regard as expressions of a metaplasia of basal cells have anything to do with a regeneration of the islands of Langerhans

We attempted to differentiate metaplasia of basal cells from regeneration of the islands of Langerhans histologically. Since Schultze<sup>36</sup> and Diamare<sup>37</sup> and subsequently Lane,<sup>38</sup> Bensley<sup>39</sup> and Bowie<sup>40</sup> were able to divide the cells of the islands of Langerhans into alpha, beta and gamma cells, we have a suitable means of making this differentiation.

Sections of proliferating duct epithelium showing a formation of buds which were suitable were stained by the Bensley stain. They failed to prove that these cells were similar to those of the islands of Langerhans.



Fig 3 (case 6) —Metaplasia of basal cells in a middle size pancreatic duct. It may be noted how the buds on opposite sides narrow the lumen of the duct.

hans. However, some of our sections were not suitable for staining by the Bensley stain. In addition to the absence of special granules, the lack of different cells and nuclei corresponding morphologically to the alpha, the beta and the gamma cells in the buds of the ducts speaks for a distinction between the metaplasia of basal cells of the ducts and a regeneration of the islands of Langerhans.

36 Schultze Arch f micr Anat **56** 491, 1900

37 Diamare Internat Monatschr f Anat u Physiol **16** 155, 1899

38 Lane Am J Anat **7** 409, 1907-1908

39 Bensley Am J Anat **12** 297 and 388, 1911-1912

40 Bowie Anat Rec **29** 57, 1924

6 *Adenoma of the Island of Langerhans*—In one of our cases we found an adenoma which took origin from an island of Langerhans. Such tumors have on different occasions been called, "adenoma of the island of Langerhans" (Heiberg<sup>41</sup>), "true adenoma of the pancreas" (Rollett<sup>42</sup>) and "adenoma arising from island cells" (Koch<sup>43</sup>), insulome (Masson<sup>44</sup>) and other such names. This is an observation comparatively rare, since but twenty cases have been reported.

The adenoma in our case measured 7 by 8 by 6 mm. It could be clearly seen with the naked eye. It was surrounded by a distinct capsule of connective tissue. The cells were arranged in rows, which were in reticular connection. Between the cells of the islands wide capillaries and blood sinuses were seen. The cells of the tumor were entirely similar to the cells of the islands of Langerhans elsewhere in the pancreas. Otherwise the pancreas presented a formation of cysts and lipomatosis. The cysts varied in size from that of a millet seed to that of a pea. The ducts leading to the area occupied by the adenoma were lined by multilayered epithelium. This epithelium sometimes blocked the ducts almost entirely, although in other instances smaller buds occurred. A direct connection between the proliferating epithelium of the ducts and the adenoma of the island of Langerhans could not be found. Enlarged islands of Langerhans were noted. They were sometimes embedded in fat tissue. Connective tissue septums were in many places thickened.

We would suggest that in the future only those enlargements of the islands of Langerhans that can be seen macroscopically should be placed in this group. Unless the term is reserved for such grossly visible tumors, it is impossible to make a distinct differentiation between an enlarged island of Langerhans that is a simple hypertrophy and a true adenoma. We do not believe that the presence of a capsule would help in this differentiation, because in cases of chronic pancreatitis the capsule cannot be differentiated from a proliferation of interstitial connective tissue.

The question may be raised as to the possible causes of such tumors. Besides the conditions already mentioned, it has been stated that the administration of pilocarpine, arsenic, adrenalin, thyroid, phlorizine, rice and beef findings may cause hypertrophy of the islands of Langerhans. But it has recently been proved that some of these agents do not produce any such change.

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41 Heiberg. *Centralbl f allg Path u path Anat* **22** 532, 1911.

42 Rollett. *Frankfurt Ztschr f Path* **10** 268, 1912.

43 Koch. *Virchows Arch f path Anat* **216** 25, 1914.

44 Masson. *Les tumeurs*, Paris, 1923, p. 442.

In a number of our cases the metaplasia of basal cells caused retention of pancreatic secretion, extreme dilatation of the pancreatic acini and flattening of their lining cells. We believe that a metaplasia of basal cells may produce the same alterations in the pancreas as is produced by a ligation of ducts, the only difference being that in the former case the ducts may be partially patent while in the latter they are entirely obliterated. A metaplasia of basal cells in the ducts may therefore cause a stasis of pancreatic secretion which is of longer duration than that which follows on ligation of ducts. After ligation of the pancreatic ducts the retention of pancreatic secretion lasts only for a short period,

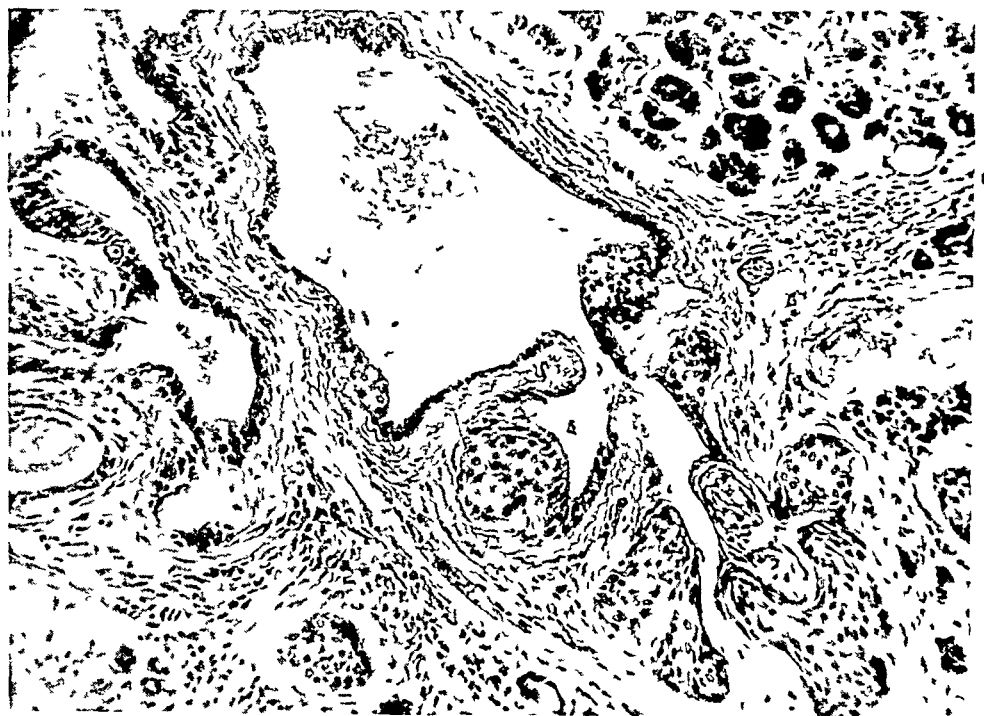


Fig 4 (case 4) —Here may be noted how the proliferation of basal cells which fills the lumen of a small pancreatic duct presents characteristics that simulate invading growth

because behind the point of ligation the cells of the acini stop secreting. If, however, the lumen of the ducts is only narrowed then the outflow of pancreatic juice is still possible and the cells of the acini will secrete for a longer period before they undergo atrophy. The irritation of the islands of Langerhans therefore continues over a longer period.

One other fact is perhaps worthy of mention. If the islands of Langerhans are to enlarge there must be sufficient room for them to do so. Thus, if there is already an increase of fibrous connective tissue around the islands of Langerhans, it is obvious that they cannot enlarge

We believe that the breaking down or colliquation of acini produces conditions which are favorable for the enlargement of the islands of Langerhans

In the twenty cases of adenoma of the island of Langerhans which we have collected from the literature, the metaplasia of basal cells in the ducts has been referred to only twice. But an accurate description of

TABLE 2—*Adenoma of the Islands of Langerhans*

Case	Recorder	Age	Sex	Size of Tumor	Diabetes	Meta- plasia of Basal Cells in Ducts	Jaundice	Gall stones
1 Nicholls	J Med Res S 385 1902			3 by 2.5 mm				
2 Helmholz	Bull Johns Hop kins Hosp 18 185, 1907	65	M	5 by 3 by 5 mm	0			
3 Morse	J A M A 51 • 1075 (Sept 26) 1908	44	F	5 mm in diameter	0			
4 Morse		46	M	3 mm in diameter	0			
5 Cecil	J Exper Med 13 • 595, 1911	63	M	4 by 3.5 mm	0			
6 Heiberg	Centralbl f allg Path u path Anat 22 532, 1911	64	F	6 by 5 mm	+			-
7 Alezais and Peyron	Compt rend Soc de biol 70 400, 1911	?	?	Of the size of a pea				-
8 Rollett	Frankfurt Ztschr f Path 10 268, 1912	25	F	11 mm in diameter	0			
9 LeComte	J Med Res 29 251, 1913 1914	42	F	100 by 70 by 40 mm	0	+		
10 Koch	Virchows Arch f path Anat 216 25, 1914	22	F	14 mm in diameter	0			+
11 Goldblatt	J Cancer Res 6 • 277, 1921	55	F	45 by 35 by 25 mm				-
12 Priesel	Frankfurt Ztschr f Path 26 453, 1922	63	F	12 by 10 by 9 mm	0			
13 Priesel		51	M	9 by 10 mm		+		0
14 Priesel		60	M	3.5 by 2.5 by 2.5 cm	0			-
15 Schneider	Contribution a l'etude de l'adenome Lan- gerhansien insulome, These, Lausanne, 1924	84	M	15 by 10 mm	0			-
16 Schneider		70	F	50 by 45 by 30 mm	0			-
17 Lang	Virchows Arch f path Anat 257 235 1925	39	F	5 mm in diameter				
18 Warren	Am J Path 11 • 335, 1926	53	F	1.7 by 1.7 by 1.4 mm	0			
19 Warren		63	M	1.3 by 1.1 mm	0			
20 Warren		49	F	1.2 by 1.2 mm	0			
21 Warren		48	F	9 by 6.5 by 6 mm	0			
22 Baló and Ballon	Surg Gynec Obst, to be published	56	F	7 by 8 by 6 mm	0	+	0	0

the duct system is, in many instances, not given. We are not of the opinion that the metaplasia of basal cells is necessarily followed by the formation of an adenoma of the islands of Langerhans but rather that if the conditions present are those which we have just described, one of the consequences then may, in some instances, be the formation of an adenoma. Priesel endeavored to show that an adenoma of the islands of Langerhans may arise from the epithelium of the ducts. But only in his second case was he able to demonstrate any histologic connection between the duct and the adenoma of the island of Langerhans.

THE ETIOLOGY OF THE METAPLASIA OF BASAL CELLS IN THE DUCTS  
OF THE PANCREAS

In considering the etiology of the metaplasia of basal cells in the ducts of the pancreas, local and general factors must be dealt with. Proliferation of basal cells is a subject to which Krompecher gave much attention. Although most of his investigations were along morphologic lines, Krompecher nevertheless repeatedly turned to the question of the cause of benign and malignant proliferation of basal cells. He concluded that benign proliferation of basal cells is a preliminary to cancer, and is due to the action of various toxins, bacterial in origin. Of particular importance he thought was the local action of these bacterial toxins. One must not think that Krompecher was of the belief that these toxins alone were responsible for the metaplasia of basal cells. His writings show clearly that he was rather of the opinion that the problem of the metaplasia of basal cells, like that of carcinoma, would only be cleared up by considering a combination of several factors.

Recent experimental observations tend to prove that the metaplasia of basal cells is dependent not only on local conditions but also on the general status of the whole organism. Thus Wolbach and Howe<sup>45</sup> reported that the cylindrical epithelium of the nares, larynx, bronchi, submaxillary glands, prostate, epididymis and seminal vesicles of rats and guinea-pigs is transformed to epithelium of the keratinizing type if the animals are kept on a diet deficient in vitamin A. Goldblatt and Benischek<sup>46</sup> also recently reported that such a diet is adequate to induce metaplasia in the various types of epithelium. They state that this epithelial metaplasia is of such frequency in young rats so treated, as to constitute an acceptable morphologic indication of the deficiency of this vitamin in the diet. They claim that inadequate food, provided the vitamins are supplied, does not induce the metaplasia. We feel that metaplasia of basal cells as described by Krompecher and the transformation of cylindrical epithelium to epithelium of the stratified keratinizing type are but gradations of the same process. They do not essentially differ.

Wolbach and Howe emphasized the fact that the foci of keratinizing epithelium are of multiple origin. In some organs, they also observed a formation of cysts, which they considered had resulted from the retention of secretion through obstruction of the ducts by desquamated keratinized epithelial cells.

In our series of 14 cases, jaundice was found post mortem 6 times. In three instances, it was due to what is called "catarrhal jaundice," in

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<sup>45</sup> Wolbach and Howe. *J. Exper. Med.* **43** 753, 1925, *Arch. Path.* **5** 239 (Feb.) 1928.

<sup>46</sup> Goldblatt and Benischek. *J. Exper. Med.* **46** 699, 1927.

one, to acute yellow atrophy of the liver, and in two, to the formation of a tumor. The catarrhal jaundice was of few days duration, while the jaundice in the cases of tumor extended for a much longer period. So, too, the metaplastic changes noted in the pancreas in cases of catarrhal jaundice were less extensive and less marked than when the jaundice had been of longer duration, as in the case of tumor. It was also to be noted that jaundice had been present at some time in the four cases of cholelithiasis, but this could not, as in the other six instances, be demonstrated at necropsy. This therefore makes a total of ten cases in which jaundice had at sometime been noted.

We observed metaplasia of basal cells in the pancreatic ducts in 87.5 per cent of all the cases which we examined. In five sevenths of these jaundice existed. The importance of jaundice is that simultaneously with it can occur the retention of pancreatic secretion from which an ascending inflammatory process in the pancreas can result. On this basis, retention of pancreatic juice, an ascending infection, or both, can be responsible for the metaplastic changes.

Can the retention of pancreatic secretion alone bring about metaplasia of basal cells in the ducts of the pancreas? A reply to this question can be given only by considering the consequences of a ligation of ducts. Kyle and Weichselbaum found that the epithelium in the pancreatic ducts of animals proliferates shortly after the ducts have been ligated. They interpreted these changes as expressions of regeneration on the part of the islands of Langerhans.

Whether the proliferation of the epithelium in certain portions of the duct or under certain conditions leads to regeneration of the islands of Langerhans or to metaplasia of basal cells is a subject for further consideration. Suffice it to say that with special stains it is possible to differentiate the different cells of the islands of Langerhans from proliferating basal epithelium. The data available to date do not consider this point.

One must also decide whether or not an ascending inflammatory process takes place in the duct system of the pancreas after ligation of the duct. We conclude that the observations in experiments with animals do not speak against the possibility that metaplasia of basal cells in the ducts of the pancreas can result from the retention of pancreatic secretion plus an ascending infection. We have demonstrated signs of an ascending infection in our acute, as well as in our chronic cases. In the acute cases these were focal necrotic areas, in the chronic lipomatosis. Lipomatosis is, in general, classified with chronic pancreatitis. Evidently the metaplasia of basal cells must be of a certain degree and duration to produce consequences in the pancreas. It is also true that not all ascending inflammations in the ducts of the pancreas bring about a metaplasia of basal cells. We examined several pancreases

in which signs of the former were evident but metaplasia of basal cells was absent

In two sevenths of our cases, local causes, such as retention of pancreatic secretion or ascending inflammation, could not be demonstrated. We must therefore believe, as we have already noted, that not only local factors but also general ones may be responsible for basal cell changes in the pancreatic duct system. What these may be besides a deficiency in vitamin A we cannot tell.

It is interesting to note that metaplasia of basal cells in the ducts of the pancreas can occur also in younger persons. Other authors have stated that, in general, such changes in the ducts of the pancreas are usually noted in advanced age, according to Priesel, in most instances, in the seventh decade. In our own series it was noted in persons under 40 years, in six instances (42.85 per cent). It must of course be appreciated that such a figure will vary considerably if the necropsies from which material is drawn also include necropsies on children. Wilson and Du Bois<sup>47</sup> have reported metaplasia of basal cells in the ducts of the pancreas of a five months old child who had died from keratomalacia.

#### SUMMARY

Metaplasia of basal cells in the ducts of the pancreas was noted in 14 (87.5 per cent) of 160 pancreases, which were examined. Metaplasia of basal cells can occur in smaller or larger ducts, forming either circumscribed "buds" or an involvement of the epithelium of the ducts in its entire circumference. Varying directly with the size of the ducts involved, either dilatation of the end chambers or formation of cysts may result.

Metaplasia of basal cells in the duct system of the pancreas may be responsible for changes which are either acute or chronic. The acute are those which result from the retention of pancreatic secretion. They may be focal necroses. The chronic changes are similar to those which ensue after experimental ligation of the pancreatic duct. Lipomatosis of the pancreas may be one of them.

The blockage of pancreatic ducts by proliferative changes of the basal cells causes enlargement of the islands of Langerhans and in one instance which we report, an adenoma of an island. Proliferating basal cells in the ducts of the pancreas do not take the special stains used to differentiate the various cell types which make up an island of Langerhans.

In five sevenths of the cases which we report, jaundice had occurred at some period. This would suggest that in the majority of cases, either a retention of pancreatic secretion, an ascending inflammatory process or

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47 Wilson and Du Bois. *Am J Dis Child* 26:431 (Nov.) 1923.

both are present, and as local factors favor the basal cell changes. In two sevenths of our cases, local factors which would adequately explain the metaplasia of basal cells could not be found. It is possible that general factors similar to a deficiency of vitamin A may play some rôle in the proliferation of basal cells in the ducts of the pancreas.

Metaplasia of basal cells in our series occurred quite frequently in young persons.



# MULTIPLE HEMANGIOMAS OF THE SKIN AND OF THE INTERNAL ORGANS\*

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In the group of angiomatous tumors a form is sometimes referred to as offering great diagnostic difficulties because it behaves like a malignant tumor although the microscopic picture is not suggestive of it. These tumors have been used as an argument in favor of the conception expressed by some pathologists that there exists an essential similarity between innocent and malignant blastomas (Shennan,<sup>1</sup> Cathcart<sup>2</sup>). The signs of malignancy of the microscopically benign but potentially malignant angiomas are their local invasive and destructive growth, their recurrence after surgical removal and their production of metastases to distant organs. There is, however, no uniformity of the histologic structure of these angiomas. Some of them grow by sprouting of capillary blood vessels, which later becoming filled with blood, expand and cause a pressure atrophy of the invaded structures. They are simple cavernous hemangiomas with practically little if any, stroma and a flat lining endothelium (Andrejew,<sup>3</sup> Berenbruch,<sup>4</sup> Hildebrand,<sup>5</sup> Konjetzny,<sup>6</sup> Schweizer,<sup>7</sup> Weiss,<sup>8</sup> Topfer,<sup>9</sup> and others). There is a second group represented by a more complicated type which shows a cellular or syncytial stroma sometimes described as embryologic. The blood vessels differentiate from this stroma and in places may become so abundant as to obscure it (Borrmann,<sup>10</sup> Ewing,<sup>11</sup> von Falkowski,<sup>12</sup> Livingston and Klempeier,<sup>13</sup> Klinge,<sup>14</sup> Shennan,<sup>1</sup> Stamm<sup>15</sup>). In some

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<sup>1</sup> From the Department of Pathology, University of Illinois College of Medicine.

1 Shennan T. J. Path. & Bact. **19** 139, 1914.

2 Cathcart, quoted from Shennan (footnote 1).

3 Andrejew. Deutsche Ztschr. f. Chir. **201** 320, 1927.

4 Berenbruch, K. Inaugural Dissertation, Tübingen, 1890.

5 Hildebrand. Deutsche Ztschr. f. Chir. **30** 91, 1890.

6 Konjetzny, G. E. München med. Wchnschr. **59** 241, 1912.

7 Schweizer, R. Schweiz. med. Wchnschr. **4** 243, 1923.

8 Weiss, S. Med. Klin. **7** 1273, 1911.

9 Topfer, D. Frankfurt Ztschr. f. Path. **36** 337, 1928.

10 Borrmann, R. Ziegler's Beiträge **40** 373, 1907.

11 Ewing, J. Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922.

12 Von Falkowski, A. Ziegler's Beiträge **57** 385, 1914.

13 Livingston, S. F., and Klempeier, P. Arch. Path. & Lab. Med. **1** 899 (June) 1926.

14 Klinge, F. Deutsche Ztschr. f. Chir. **183** 195, 1923.

15 Stamm, R. Inaugural Dissertation, Göttingen, 1891.

instances, a marked hyperplasia and proliferation of the endothelium have been observed (Shennan,<sup>1</sup> Stamm<sup>15</sup>) with a differentiation of the large endothelial cells into blood cells (von Falkowski,<sup>12</sup> Klinge<sup>14</sup>) One fully agrees with Klemperer that in the presence of such microscopic observations one should not speak of a benign tumor, although anaplasia of the cells is not present These cases prove that malignancy cannot be considered simply from the standpoint of the cellular structure There are, also, transitional stages between these forms of hemangiomas and sarcomatous angiomas, which are vascular tumors with a sarcomatous stroma (Jores,<sup>16</sup> Langhans,<sup>17</sup> Theile,<sup>18</sup> Ramdohr<sup>19</sup> and others)

Association with what were supposed to be metastases was observed in both groups of hemangiomas, in the simple cavernous (Konjetzny,<sup>6</sup> Weiss<sup>8</sup>) as well as in those with embryonic stroma (Borrmann,<sup>10</sup> Klinge,<sup>14</sup> Shennan,<sup>1</sup> Stamm<sup>15</sup>) In the cases described by Livingston and Klemperer<sup>13</sup> and Ewing,<sup>11</sup> postmortem examinations had not been made, but in the latter case an involvement of the lungs was suggested by the clinical observations At least as far as the hemangiomas with a mature stroma are concerned, their possible formation of metastases is doubtful Multiplicity of hemangiomas of the skin and mucous membranes is common, and is explained by the fact that the hemangioma is a congenital formation the origin of which can be traced to the first anlage of the vascular system in early embryonic life (Ribbert<sup>20</sup>) The occasional appearance of these tumors in later life, as in familial epistaxis (Goldstein,<sup>21</sup> Osler,<sup>22</sup> Steiner,<sup>23</sup> Williams,<sup>24</sup>), does not speak against their congenital character, which is also evident from the heredity Hemangiomas of the skin not seldom occur with similar tumors of the liver (Bruchanow,<sup>25</sup> Roggenbauer,<sup>26</sup> Fischer<sup>27</sup>) An interesting condition, described as Lindau's disease,<sup>28</sup> presents cystic angiomas of the cerebellum associated with an angiomatosis of the retina (von Hippel's disease) angiomas of the spinal cord, cystic formations

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16 Jores, L Centralbl f allg Path u path Anat **19** 662, 1908

17 Langhans, T Virchow's Arch f path Anat **75** 273, 1879

18 Theile Virchow's Arch f path Anat **178** 296, 1904

19 Ramdohr, M Virchow's Arch f path Anat **73** 459, 1878

20 Ribbert, H Geschwulstlehre Cohen, 1911

21 Goldstein, H I Arch Int Med **27** 102 (Jan) 1921

22 Osler, W Bull Johns Hopkins Hosp **12** 333, 1901

23 Steiner, Arch Int Med **19** 194 (Feb) 1917

24 Williams, C M Arch Dermat & Syph **14** 1, 1926

25 Bruchanow Ztschr f Heilk **20** 1, 1899

26 Roggenbauer Ziegler's Beitrage **49** 313, 1910

27 Fischer, B Pathologie des Angioms, Ergebr d allg pathol u path Anat **10** 815, 1904-1905

28 Lindau, A Acta path et microbiol Scadinav, 1926, suppl 1

of the pancreas and of the kidneys and hypernephromas (Rochat,<sup>29</sup> Schuback<sup>30</sup>)

Finally, there are the cases of numerous hemangiomas in different organs, including such unusual sites as the lungs, the heart, the thyroid and the uterus. From the literature, I have collected the following combinations of sites: Skin, liver, spleen and bones of the skull (Billroth<sup>31</sup>), in a case of Lindau's disease, involvement of the base of the skull, the bone marrow and the urinary bladder (Brandt<sup>32</sup>), skin, liver, parotid gland and intestine (Gascoven<sup>33</sup>), skin, mucous membranes, mesentery and retropleural tissue (Ghon<sup>34</sup>), skin and pia mater (Kalischer<sup>35</sup>), liver and bones of the skull (Major and Black<sup>36</sup>), liver, suprarenal gland, ovaries and uterus (Payne<sup>37</sup>), skin, epicardium, pleura, peritoneum and choroid plexus (von Rokitsansky<sup>38</sup>), skin, mucous membranes, liver and heart (Runge<sup>39</sup>), cerebellum, medulla oblongata, spinal cord, liver and urinary bladder (Tannenbeig<sup>40</sup>), (1) skin, mucous membranes, submaxillary gland, thyroid, liver, lung, intestine and urinary bladder and (2) skin, mucous membranes, mediastinum, pericardium, liver and left kidney (Topfer<sup>41</sup>), skin, mucous membranes, peritoneum and liver (Ullmann<sup>42</sup>) and liver and bones of the skull (Virchow<sup>43</sup>)

To these cases I wish to add a new one which is of interest especially with regard to the question of metastasizing

#### REPORT OF A CASE

*History*—A white girl, aged 4 days, was brought to the Cook County Hospital by her father, who said that at birth a marked swelling of her neck had been noted. The family history and the details of the birth of the child were not significant.

The clinical examination showed a female infant 44 cm long and 2.6 Kg in weight. On the left side of the neck was a large, purplish gray tumor-like mass,

29 Rochat, G. F. *Klin Monatsbl f Augenh* **78** 601, 1927

30 Schuback, A. *Ztschr f d ges Neurol u Psychiat* **110** 359, 1927

31 Billroth, T., quoted from Veeber, B. S., and Austin, I. H. *Am J Med Sc* **143** 102, 1912

32 Brandt, R. *Graefe's Arch f Ophth* **106** 127, 1921

33 Gascoven. *Tr Path Soc London* **2** 267, 1860

34 Ghon, A. *Verhandl d Deutsch Path Gesellsch* **12** 242, 1908

35 Kalischer, S. *Arch f Psychiat* **34** 171, 1901

36 Major, R., and Black, D. R. *Am J Med Sc* **156** 469, 1918

37 Payne. *Tr Path Soc London* **20** 203, 1869

38 Von Rokitsansky, C. *Manual of Pathological Anatomy*, Blanchard and Lea, Philadelphia, 1855

39 Runge, H. *Arch f Gynak* **122** 491, 1924

40 Tannenbeig, J. *Ztschr f d ges Neurol u Psychiat* **92** 119, 1924

41 Topfer, D. *Frankurt Ztschr f Path* **36** 337, 1928

42 Ullmann, K. *Sitzungsb d Ges d Arzte Wien*, March 10, 1899

43 Virchow, R. *Die krankhaften Geschwulste*, Berlin, 1863

which reached from the anterior median line to the posterior margin of the left sternocleidomastoid muscle and from the shoulder joint to the mastoid region, pushing up the left ear. The tumor was sacculated, soft and compressible. The skin was not adherent, there were not any thrills or pulsations. From the tumor, pure blood was aspirated which gave a negative Wassermann reaction.

Scattered over the body in the skin were about 100 small nodules varying in size from that of a pinpoint to that of a diameter of 1 cm. These were purple, sometimes with a gray tint. The nodules were elevated over the skin and were firm.

The child had a persistent discharge from the vagina, in which on several occasions gram-negative diplococci resembling gonococci were found. After the child had been in the hospital eight months, it contracted measles, from which it recovered. During the entire period of observation the tumor in the neck remained unchanged.

The patient was discharged from the hospital, but was brought back a month later acutely ill with fever, restless, and refusing food. A diagnosis of lobular pneumonia of the right upper lobe was made. The tumor of the neck had greatly decreased in size. The overlying skin was wrinkled, and a baggy mass was felt under it. The purple nodules of the skin still were present.

The infant was transferred to the Research and Educational Hospital of the University of Illinois. It grew weaker rapidly and developed an acute suppurative condition of the right thigh. The temperature went up to 106 F. A spinal puncture made immediately before death showed a turbid fluid under increased pressure, which gave a positive reaction in the Ross-Jones test and which contained 800 leukocytes per cubic millimeter. Cultures made from this fluid yielded hemolytic streptococci.

*Autopsy*—The body was that of a poorly nourished white girl, 68 cm long and weighing 4,800 Gm. The skin was studded with sharply demarcated, dark violet, round patches, varying from 1 to 4 mm in diameter. These patches were most numerous on the right side of the face, around and inside the right ear, on both sides of the chest and on the left side of the back. Though scanty on the extremities, they were also found on the soles of the feet and on the palms of the hands. In the right groin, a fluctuating swelling was present. The skin over the left side of the neck appeared wrinkled, and a dense mass was felt underneath it. This mass contained several hard nodules.

On removal of the soft parts of the head, a cavity was discovered between the galea aponeurotica and the lower posterior angle of the right parietal bone. The cavity contained thick, dark yellow pus, which extended through an irregular penetrating defect in the bone to the external surface of the dura mater. The internal surface of the dura was smooth and shiny.

At the base of the brain, much thick yellow pus had accumulated. Pus covered also the convex surface of the hemispheres, being most abundant near the medial margin and about the poles of the temporal lobes. In the region of both sylvian fissures, a deep blue mass shone through the opaque leptomeninges. The mass covered the lower third of the posterior central convolution and extended backward to the interparietal sulcus. When these areas were cut through, there was revealed the presence of dilated and convoluted, thin walled blood vessels, which were from 1 to 2 mm thick. The brain was soft, the ventricles were dilated and filled with much cloudy fluid.

The accumulation of pus in the subarachnoidal spaces continued into the spinal canal. The inside of the dura mater showed, in its ventral aspect, at the height of the upper cervical region, a number of flat, deep blue elevations, filled with blood. The anterior roots of the second and third cervical nerves were thicker than they normally are and grayish red.

Dissection of the left side of the neck exposed a firm fibrous mass, covered by but not fixed to the skin, extending from the clavicle to 3 cm below the mastoid bone. This mass was adherent to the superficial fascia. It contained several calcified nodules.

The thyroid weighed 25 Gm. It was grayish brown and firm. It contained a number of deep red, round areas measuring from 0.5 to 1.5 mm in diameter.

The thymus was made up of firm, grayish white tissue, and weighed 2 Gm.

The lungs were free. The surface appeared a light grayish red. The interlobular septums were distinct as white lines. Scattered over both lungs were numerous deep red, slightly elevated, round areas from 0.5 to 3 mm in diameter (fig 1). They were located in the interlobular septums. About fifty of these patches were counted on the surface of each lung. The lungs were filled with air except for some irregular areas along the anterior margin of both the upper and the lower lobes, where the tissue was firm and deep grayish red.



Fig 1—The left lung, showing multiple subpleural hemangiomas

The heart weighed 35 Gm and was of normal shape. Changes were not observable in the valves, the intima of the aorta was smooth. The small intestine, on the surface, showed many irregularly shaped, dark red patches, varying in diameter from 2 to 6 mm, which were located opposite the mesenteric attachment (fig 2). The patches were composed of tortuous tufts located in the wall and shining through the serosa and mucosa. The sigmoid, near the anterior margin of the mesocolic attachment, contained a mass of convoluted vessels. This mass was 18 mm long, 15 mm wide and from 5 to 7 mm thick. It contained a few small, stony concretions.

The liver weighed 238 Gm, the spleen 18 and the pancreas 7. These organs did not reveal anything unusual. The same can be said about the suprarenal gland, the kidneys, the stomach and the sex organs.

In the left groin, an extensive suppuration extended between the adductor muscles down into the region of the median epicondyle.

The bone marrow in the middle of the right femur was soft and reddish brown

Smears made from the pus between the leptomeninges and in the groin showed numerous long chains of streptococci

*Microscopic Examination*—The violet patches of the skin were wide, blood-filled spaces located in the subepidermal part of the cutis. They were lined by a flat endothelium and were derived from capillary vessels, which opened into them abruptly. Similar, smaller blood-filled spaces were present in the deeper layers of the cutis, where they often arranged themselves about the sweat glands.

The convoluted masses of the leptomeninges, which filled the sylvian fissures, were composed of wide blood vessels. The walls of these vessels were formed by from two to three layers of fibrillar connective tissue lined by a flat endothelium (fig 3). The vessels were filled with blood, which in places had coagulated. From them originated narrow branches which entered the cortex of the brain. The blood vessels in the brain did not show abnormal widening. Between the leptomeninges there was much exudation consisting of a network of fibrin and polymorphonuclear and mononuclear cells.



Fig 2—The small intestine, showing multiple hemangiomas

Transverse sections through the right parietal bone showed a filling of the spaces of the diploe by loose, fibrillar connective tissue, in which were embedded numerous wide and thin-walled blood vessels. Here and there a small group of myelocytes was found. The bone appeared normal.

The body of the third cervical vertebra contained active bone marrow with small foci of degeneration and an intracellular accumulation of fibrinous exudate. Abnormal widening of the blood vessels was not seen.

In the ventral portion of the upper cervical dura mater were numerous round and oval blood-filled spaces. They were located near the internal surface and protruded somewhat into the spinal canal.

In the spinal cord a diffuse capillary hyperemia and degenerative changes of the ganglion cells of the anterior horns were observed. The blood vessels appeared normal. The anterior roots of the upper cervical nerves, described macroscopically as thickened and reddish gray, showed a striking predominance of the blood vessels (fig 4). The vessels divided dichotomically, ran parallel with the nerve fibers, from which they were separated only by a flat endothelium, and occupied almost one fourth of the transverse diameter of the nerve.

In the thyroid, the interlobular septums were thicker than normal and contained many wide blood vessels of various shapes (fig 5) These vessels extended into the lobules and came in close contact with the follicles, which showed signs of compression The shape of the vessels depended on their size, that is, the smaller vessels were of irregular shape with lakelike outlines and gave off branches which



Fig 3—Hemangioma of the leptomeninges in the region of the sylvian fissure Between the leptomeninges there is purulent exudation Magnification, 15 times



Fig 4—Hemangioma of the left anterior root of the third cervical nerve Magnification, 25 times

originated from them with a funnel shaped widening The larger spaces were round or oval and were connected only with an afferent and an efferent vessel The largest spaces often contained coagulated blood with beginning organization of the thrombus All the spaces had a lining of flat endothelium

The pleura of the lung was composed of several layers of fibrillar connective tissue Where the interlobular septums were given off, round or oval blood-filled

spaces were present, which often bulged into the adjacent alveolar spaces. The alveoli bordering the septums had thick walls and were narrow, while near the center of the lobules the alveoli were wide. The dense areas near the anterior margins contained cellular exudate.



Fig 5—Hemangioma of the thyroid. Compression of the follicles is shown. Magnification, 120 times.

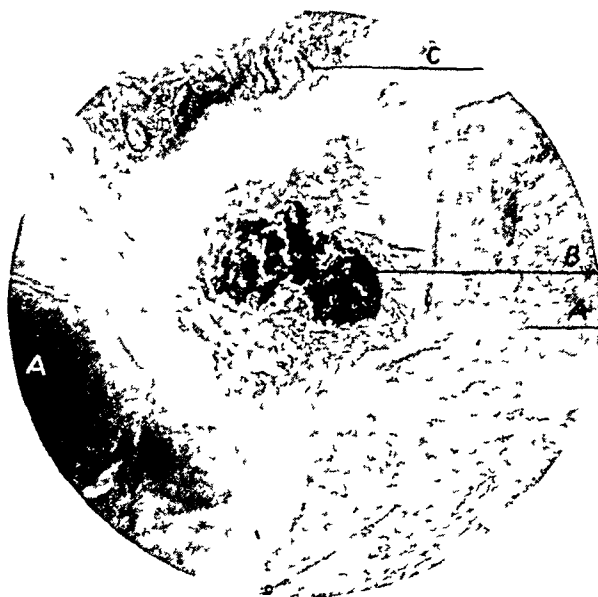


Fig 6—Hemangioma of the sigmoid. *A* indicates spaces filled with blood in the submucosa and the muscularis, *B*, a calcified thrombus, and *C*, mucosa. Magnification, 60 times.

The submucosa of the small intestine was distinctly thicker than normal and contained wide blood-filled spaces which compressed the muscularis. The spaces showed baylike extensions, which led into capillary blood vessels that ran towards the mucosa. In some of the spaces, recently formed thrombi were attached to the



lining of flat endothelium. The distribution of the vessels was best studied on small pieces of the intestinal wall, cleared and mounted in toto. In these preparations, straight and narrow vessels were seen running parallel to the surface. They widened suddenly and formed coils, from the convexity of which the smaller branches originated. Single coils were much distended and appeared as blood-filled lakes.

The abundance of the blood vessels was most marked in the portion of the sigmoid described as a convoluted, dark violet mass. The intestinal wall here consisted chiefly of blood vessels, which also occupied the muscularis and produced nodular projections on the serosa. The mucosa was thin and atrophic. Many of the wide vessels contained blood clots. These clots underwent calcification and led to the formation of stony concretions embedded with dense connective tissue (fig. 6).

In the spleen, a few round or oval blood-filled spaces were found about the follicles. The latter were small and often contained a center composed of epithelioid cells with granules of hemosiderin.

Abnormal blood vessels were not found in the kidneys, suprarenal glands, ovaries, and pancreas.

*Anatomic Diagnosis*—Purulent streptococcal meningitis, subcutaneous abscess in the right posterior parietal region with erosion of the parietal bone and external pachymeningitis, deep phlegmon of the left thigh, confluent bronchopneumonia in both lungs, accidental involution of the thymus, fatty infiltration of the liver, cloudy swelling of the kidneys, and multiple hemangiomas of the skin, the leptomeninges, the anterior roots of the cervical nerves, dura mater spinalis, the diploe of the parietal bone, the thyroid, the lungs, the intestine and the spleen.

#### COMMENT

Studying the microscopic sections of this case, one obtains the impression that in many organs there was a marked disproportion between the development of the blood vessels and that of the specific structures. The blood vessels seemed to have grown much the faster and this excessive growth affected both their length and their circumference. They became too long and too wide, forming tortuous coils and lakelike spaces of blood. The tortuous portions gave off branches, while the wide spaces were connected only with an afferent and an efferent capillary blood vessel. Endothelial hyperplasia was not present.

In the introduction it was mentioned that in some hemangiomas the newly formed vessels differentiate from an indifferent cystogenic mesenchyma. I have recently seen two such tumors in animals. One was a mixed hemangio-lymphangioma which had replaced large portions of the liver of a dog and had also involved the ligamentum hepatoduodenale and a group of lymph glands at the hilum of the liver. The second tumor was one in a cow shown to me by Dr. E. Day. In both lungs of the cow, there were multiple angiomatous tumors composed of a markedly cellular stroma from which blood vessels developed through blood cells accumulating between the spindle-shaped cells and pushing them apart. Such stroma was not present in the multiple hemangiomas

of the child, although in some organs, especially in the lungs, the intestine and the thyroid, the abnormal growth of the blood vessels was associated with a marked increase of the surrounding connective tissue. This connective tissue, however, was mature, without any blood vessel and blood cell forming potencies, as in the cases reported by von Falkowski,<sup>12</sup> Klinge<sup>14</sup> and others. The angiomas arose from the preexistent capillary blood vessels by a giant growth of more or less circumscribed segments.

One may ask whether a lesion of this character should be classified as a hemangioma, a term which means a true vascular tumor. It is difficult to draw a sharp borderline between angiomas and angiectases, but in the presence of signs of an active growth, as compression and involvement of the surrounding structures, the determination of a vascular formation as tumor cannot be objected to. This tumor is a hamartoma with a tendency to continuous growth, although this tendency may be insignificant.

Some of the hemangiomas showed signs of spontaneous regression. There was a thrombosis of the wide blood-filled spaces with organization and calcification, which terminated in the complete obliteration of these spaces. The child had been suffering from repeated severe infections, it is known that intercurrent diseases may initiate the regression of hemangiomas.

Many of the patients afflicted with multiple hemangiomas die in early childhood, whatever the microscopic picture of the tumors may be (Bruchanow,<sup>25</sup> von Falkowski,<sup>12</sup> Kalischer,<sup>35</sup> Konjetzny,<sup>6</sup> Ramdohr,<sup>19</sup> Runge,<sup>39</sup> Stamm,<sup>15</sup> Topfer,<sup>9</sup> Weiss<sup>8</sup>). If the patients attain a later age, some of the tumors may have reached a considerable size, since they keep on growing. There is a difference in the rate of growth, some of the multiple tumors growing faster than others. Even at the time of birth, there is a marked difference in the size and the extension of the angiomas. Thus, in my case, the swelling of the neck was first the outstanding feature, which later decreased considerably, but at the autopsy table the most pronounced vascular changes were found in the leptomeninges and in the sigmoid. In the spleen, they were visible only under the microscope. The predominance of the vascular new growth in one region of the body does not indicate that this new growth is the primary tumor and that the smaller formations scattered over the other organs are metastases. It is much more likely that all the tumors arose at the same time independently of each other. It is not necessary to assume that blood vessel formation elements are transplanted from a primary focus by way of the blood or lymph stream to a distant organ. Indeed this implantation has never been demonstrated even in the cases of hemangiomas with an indifferent stroma and hyperplastic endothelium.

The multiple cellular hemangiomas in the lung of a cow, which were mentioned, could be traced to small islands of a cellular mesenchyma which were found in the corners of the alveolar septums and around the smaller bronchi and which did not show evidences of a metastatic origin

#### SUMMARY

A case of multiple hemangiomas of the skin and the internal organs in an infant is described. There was a marked difference in the size of these tumors, which in some organs showed signs of expansive growth. In spite of these observations, all the tumors were considered to be simultaneous and independent formations. The existence of a so-called benign, metastasizing hemangioma is doubtful.

# DIFFUSE, OBLITERATING ENDARTERITIS OF UNKNOWN ETIOLOGY

AN INSTANCE WITH OBLITERATION OF THE INFERIOR VENA CAVA \*

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This communication concerns an unusual instance of a diffuse, obliterating proliferation of the intima of the medium-sized and smaller arteries of the brain, heart, lungs, spleen, kidneys, thyroid and extremities associated with complete occlusion of the inferior vena cava. This widespread obliterative process resulted in profound anatomic changes in the viscera involved, with concomitant protean clinical manifestations. The process in all the vessels was limited almost in its entirety to the intima. We are unable to establish the exact nature of the process.

Bronson<sup>1</sup> reported an instance of diffuse obliterative arteritis of the vessels of the extremities, kidneys and brain in a boy aged 12. The patient did not show evidence of syphilis. The right kidney was irregularly contracted, the left was larger than normal but did not show any other change. There was a widespread obliteration of the small arteries and arterioles due to proliferation of the intima only, with atrophic changes in the parenchyma.

A thorough search of the literature did not reveal another similar instance.

## REPORT OF A CASE

*History*—A woman, aged 47, entered the Montefiore Hospital on Dec 11, 1927, complaining that the left side of the body had been weak for one year and that she had been unable to read, write or understand spoken language for three years. She had been married thirty-two years and had had two children, the younger aged 29. After the birth of her second child, she had had five miscarriages. Five years before admission she had developed a varicose ulcer, which had healed slowly. About the same time she became increasingly irritable and one year later suddenly lost the ability to write. Subsequently, her understanding of spoken and written words rapidly disappeared. About this time, she complained of compression pains over the precordia, which were severely aggravated by slight exertion. Two years later she had a "stroke" and developed a complete left sided hemiplegia with diplopia, aphasia and inability to swallow properly. Her condition improved in the course of the next three weeks. However, she lost interest in her friends and became emotionally unstable. She continued to complain of precordial pain.

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\* From the Division of Laboratories, Montefiore Hospital.

<sup>1</sup> Bronson, W. P. S. Obliterative Arteritis, *Tr. Path. Soc. London* **55**: 212, 1905.

on slight exertion. During the few weeks prior to her admission, she had several peculiar attacks consisting of rigidity of the muscles of her trunk and extremities, accompanied by snorting respiration. During one of these attacks the patient had a chill and transient dimness of vision, and lost her ability to recognize objects or their use.

*Physical Examination*—The patient was moderately obese and emotionally unstable. The superficial veins of the abdomen, groins and upper half of the thighs were markedly dilated and tortuous. A slight cyanosis of the lips was present. The left pupil was larger than the right, though both reacted to light and accommodation. The sclera had a subicteric tint. The heart was enlarged to the left, murmurs and other irregularities were not noted. The pulses were equal and regular, the blood pressure was 110 over 80. The lungs were normal. Healed ulcerations were present on both legs.

There was a mixed aphasia, also apraxia, left-sided astereognosis, emotional instability and residual signs of left hemiparesis with a questionable pseudobulbar speech.

The urine was normal. There was a slight secondary anemia. The Wassermann test of the blood was four plus, of the spinal fluid, negative. An x-ray photograph of the heart showed enlargement of all the chambers. The results of the chemical examination of the blood were normal.

The clinical diagnosis was cerebrospinal vascular syphilis.

*Course*—The patient left the institution unimproved. She continued to complain of shortness of breath. On one occasion she expectorated clots of dark reddish-brown blood. On a return visit for antisyphilitic treatment, she suddenly developed a right hemiplegia. A few days later the temperature rose to 101 F. The pulse and respirations were rapid. She became drowsy. Coarse, moist rales were heard over both bases of the lungs. She died with pulmonary edema on Jan 19, 1928.

*Autopsy*—Examination of the body ten hours after death showed generalized endarteritis (possibly syphilitic), occlusion of the descending branch of the left coronary artery, healed infarct of the left ventricular wall, multiple infarcts of the brain, organized thrombosis, with complete occlusion of the inferior vena cava from the level of the renal veins to the femoral veins, healed infarct of the lung, healed infarct of the spleen, ulcers of the leg, multiple adenoma of the thyroid, primary contracted kidneys (arteriosclerosis), and acute purulent leptomeningitis.

On the external surfaces of both legs were several small ulcerated areas. The large toes of both feet were deep bluish black. The lower abdominal veins were prominent and tortuous.

The heart weighed 400 Gm. All the chambers were dilated, and the muscle was hypertrophied. The myocardium showed numerous fibrotic streaks. In the right ventricle, a large, lamellated, irregular, yellowish-white mass, 6 cm by 3 cm, was closely adherent to the anterior surface of the lower half of the ventricular wall. Beneath this, the heart muscle was thinned down to about 3 mm and was densely scarred. The layers of the pericardium over this area were adherent. The interventricular branch of the left coronary vessel, for a distance of 3 cm from its opening, was completely obliterated by a yellowish-white, firmly adherent mass.

The right kidney weighed 100 Gm, the left 80 Gm. The capsules stripped with slight difficulty. Both kidneys were firm, deep red, and the surface was coarsely granular. On section, the cortex was found to be narrow, the glomeruli were indistinct.

A few linear streakings and irregular yellowish plaques were present in the intima of the ascending portion of the aorta and in the abdominal aorta just distal to the mesenteric vessels. The inferior vena cava, from its origin to just below the entrance of the renal veins, was completely occluded by a firm, grayish-white, adherent mass which tapered for a distance of several centimeters above the point of complete occlusion. The vein in its greater portion was a fibrous cord. The common iliac veins were involved in the process, and the left renal vein was partly occluded by organized mural masses.

Several well defined nodules were found in the thyroid gland. On section, these appeared yellowish-brown, some were cystic.

The other organs did not show abnormalities.



Fig 1—A section of coronary vessels, magnified 10 times, showing marked proliferation of the intima of several branches with almost complete obliteration of the lumen.

The meninges over both convexities of the brain were infiltrated with greenish pus, which was apparently confined to the subarachnoid space. Both occipital regions were atrophied with softening in the right and left parietal regions. The blood vessels did not show any arteriosclerotic changes. In both hemispheres, there was softening extending from approximately the sylvian fissure back to the occipital pole. Ventrally, this softening extended into the upper thirds of the right and the left putamen and of the right thalamus. The capsule was more involved on the right than on the left. The ventral half of the neostriatum and of the thalamus were grossly intact, as well as the corpus callosum. A cyst 0.5 cm in diameter adjoined the left calcarine fissure. In horizontal sections through the corpus callosum and the upper third of the caudate nucleus, appeared two areas of organized softening in the left hemisphere, one destroying the posterior third of the left frontal lobe and extending far into the corona radiata, and the other in the posterior half of the parietal region mainly confined to the cortical layers with

smaller foci irregularly distributed in the cortex of the right central parietal and occipital regions. In the section through the striatum, pallidum and thalamus, and the upper third of the cerebellar vermis, the whole parietal lobe was destroyed in the left hemisphere.

The spinal cord was grossly normal.

*Microscopic Examination*—In the heart, at the site of the infarct, the muscle was thinned out and practically replaced by fibrous connective tissue. Beneath this, the muscle fibers contained a considerable amount of fat, the nuclei were pyknotic. On the endothelial surface of the infarct, there was an organized thrombus fused with the underlying fibrous plaque. Other sections of the myocardium showed fibrotic streaks and small foci of round cells in the interstitial tissue. An arteriole was obliterated by a mass of fibrous tissue which contained a small space lined



Fig 2—A section of the lung, magnified 40 times, showing complete obliteration of the lumen of a small artery with recanalization. Signs of acute bronchitis appear close to the vessel.

with endothelium. The coronary arteries showed extensive obliteration by masses of connective tissue, which extended directly from the intima and were continuous with it. There were spaces lined with endothelium in these occluding masses. The connective tissue contained a few cellular elements. The elastic coat was intact, the entire process being limited to the intima.

The bronchi were filled with pus, the mucosa was in part desquamated. There were small abscesses in the parenchyma of the lungs, edema and congestion were present. Several of the pulmonary vessels were partly occluded by thickening of the intima. A few small arteries were filled with a mass of connective tissue containing several large spaces lined with endothelium. The smaller spaces were not surrounded by a layer of elastic tissue.

In the liver, there was slight cloudy swelling, but changes were not observable in the vessels in the sections examined.

In the spleen, congestion and a scant cellularity of the pulp were observed. The malpighian corpuscles were small. The arterioles in the corpuscles and the small arteries showed a striking proliferation of the intima, which in many instances completely filled the lumen. The elastic layer was somewhat thickened in some of the vessels. Several small, healed infarcted areas were seen and one recent hemorrhagic infarct.

The cortex of the kidneys was markedly narrowed. The arterioles and the small and medium sized arteries showed extensive changes, particularly of the intima. The lumen of some of the vessels was narrowed to a mere slit, in others it was completely occluded by a mass of connective tissue in direct continuity with the intima, sparsely cellular, and containing one or two spaces lined with endothelium. Pigment was not present in the mass. The elastic coat of the arteries

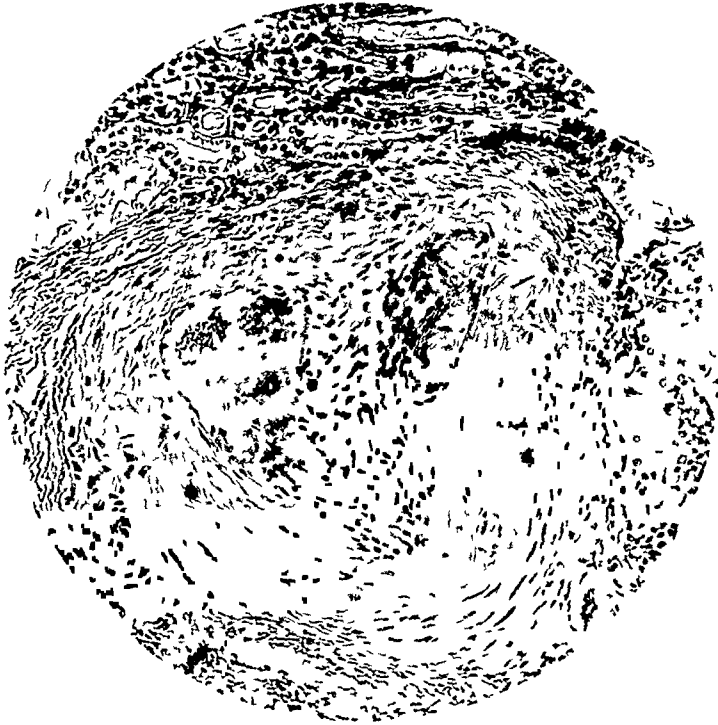


Fig 3—A section of the kidney, magnified 20 times, showing a mass of connective tissue extending from the intima and filling the lumen of a small artery. Blood spaces lined with endothelium may be seen in the occluding mass.

was intact and, in places, strikingly thickened. The glomeruli were, in places, completely replaced by concentrically arranged lamellae of connective tissue. All gradations were seen, from moderate thickening of Bowman's capsule to complete replacement of the tuft by connective tissue. The accompanying tubules were atrophic, some contained a homogeneous material that stained pink. The interstitial connective tissue was increased and infiltrated with round cells. The areas of involvement occurred at more or less regular intervals in the cortex, the intervening tissue appearing normal.

There was little lipid material in the cortex of the suprarenal glands. A few of the small arterioles showed thickening of the intima.

One of the medium sized arteries and several of the small arteries and arterioles of the thyroid gland showed the same occluding, proliferating process of the intima that has been described for the other organs. One of the small veins in an area



showing the structure of a fetal adenoma was completely occluded by a mass of connective tissue containing a few spaces lined with endothelium. Blood pigment was not present in the mass. One small area was hyperplastic and was surrounded by a capsule of connective tissue. The follicles were otherwise normal in content of colloid.

The pancreas was normal.

The glands of the mucosa of the uterus were atrophic. The vessels showed marked thickening of the intima.

The ovary contained a moderate number of corpora albicantia. The vessels showed marked thickening of the intima.

In a skin section through an ulcer the epidermis was ulcerated, and the floor was lined by fibrous connective tissue. In one region of the floor, moderate infiltration with lymphocytes was observed. A small vessel in this region was completely obliterated by an occluding mass of connective tissue.

The intima of the aorta was slightly thickened in places.

The bone marrow and the breast did not show abnormalities.

In the inferior vena cava the lumen was filled with a mass of connective tissue continuous with the intima and penetrated by large spaces lined with endothelium. The mass of hyalinized connective tissue occluding the lumen was sparsely cellular. In one area of the mass, close to the line of the intimal endothelium, were a number of small comma-shaped nuclei. The larger vascular spaces contained few blood elements. The elastic lamella was, for the most part, intact. Recent inflammatory reaction and blood pigment were not in evidence.

The areas of destruction in the brain which were described grossly showed an advanced stage of organization, with a dense, vascular, granulation tissue. Besides this old process of organized softening, there was an acute suppurative inflammation of the leptomeninges, which extended along the meningeal covering of the blood vessels into the superficial layers of the cortex. Transverse sections through medium-sized and larger blood vessels traversing the meninges did not reveal any marked pathologic changes. In contrast with them, the sylvian artery showed a thickening of the intima with a simultaneous thickening of the elastica interna. Signs of recent inflammatory reaction were absent.

The spinal cord was normal.

The multiple foci of organized softening in the brain may be traced back to multiple thrombosis as a sequence of the endarterial changes. The endarteritis that has been described was not syphilitic. The absence of cellular infiltration and of a pronounced reaction of the connective tissue was atypical.

#### COMMENT

The nature of the endarterial obliterative processes has been the subject of a confusing dispute in the literature. The term "obliterative arteritis" was first introduced by Friedländer,<sup>2</sup> in 1876, to describe a proliferative process of the intima of arteries in inflammatory tissue as in tuberculosis. The arterial reaction is a secondary response to a surrounding inflammatory process. However, the repeated application of the phrase *endarteritis obliterans* or *proliferans* to arteriosclerotic or syphilitic processes of the extremities is so thoroughly established in

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<sup>2</sup> Friedländer. *Arteritis Obliterans*, *Centralblatt für medizinische Wissenschaft* 4:364, 1876.

pathologic terminology that the original connotation of the phrase has been lost. Other types of endarteritis now differentiated in addition to a syphilitic endarteritis are arteriosclerotic endarteritis, the endarteritis occurring in inflammatory tissue as in tuberculosis, and the physiologic endarterial processes such as those which occur in the ductus arteriosus and in the vessels of the uterus and of the thyroid. The morphologic variation in the reaction of the intima of a vessel is so slight that any one of a number of different varieties of pathologic or physiologic stimuli may result in the same anatomic change. The end picture does not assist in determining the etiologic factor.

In the instance reported in this paper, the sections point to a widespread obliterating process in the arterial and in part of the venous system of the body, apparently of considerable duration. Manifestations of recent inflammatory lesions were absent, as was any evidence of syphilis. Little evidence of a general arteriosclerosis of the large vessels could be found. The lesions in the vessels were apparently primarily intimal, and in the arteries consisted of a proliferative process of the connective tissue elements of the intima. With a positive Wassermann reaction and a history of repeated miscarriages, is one justified in assuming that the patient had had a syphilitic infection, and, if so, was the present pathologic picture the end-stage of a syphilitic endarteritis? In none of the sections was there any cellular reaction about the vessels such as one expects in syphilis. In none of the sections were spirochetes found. Nevertheless, this possibility cannot be excluded. It is unlikely that the condition bore more than a superficial relationship to the arteriosclerotic endarteritis of the extremities. Since arteriosclerotic endarteritis obliterans is a common condition, one would expect the disease described in this paper to occur more often.

The process, anatomically, did not show any evidence of progression, but it cannot be definitely stated that the process had been arrested. From all indications, it would seem that whatever the etiologic factors had been, they were not any longer operative. It is possible that a combination of factors was responsible, some toxin arising from the numerous abortions, as well as from syphilis, irritating the intima of the vessels.

The most marked lesions occurred in those organs which normally present a great lability of physiologic response, the uterus, thyroid, spleen and ovaries. The normal method of reducing hyperemia in these organs is by a "physiologic" obliterative endarteritis. The lesions of the vessels in the other organs in the instance described were not in any way different histologically from this physiologic reaction. It is possible that the condition was some peculiar metabolic phenomenon which manifests itself in a pathologic exaggeration of this physiologic response.

The cause of the occlusion of the inferior vena cava is not clear. The occlusion apparently was not due to thrombosis following some cause intrinsic in the vein. Pleasants,<sup>3</sup> in a survey of the instances of occlusion of the inferior vena cava in the literature, mentioned among the factors in thrombosis, infections such as typhoid and syphilis, and propagation from some area of infection such as the uterus. It is possible that syphilis played a rôle here, as well, though the occlusion of the uterine veins may indicate that a previous postpartum infection had been the initiating cause.

The occurrence of a low blood pressure in a person with a diffuse obliterative process of the small vessels can be explained on the basis of the subsequent coronary thrombosis. It is well known that the drop in blood pressure in instances of coronary occlusion remains permanent (if the patient recovers from the attack) in spite of a preceding hypertension.

#### SUMMARY

An instance of diffuse, obliterating endarteritis involving the medium sized and smaller arteries of the heart, brain, thyroid, lung, kidneys and extremities, together with an organized occluding thrombosis of the inferior vena cava in a woman, aged 47, is reported. The etiology is unknown. A single similar instance was found in the literature.

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3 Pleasants, J. H. Obstruction of the Inferior Vena Cava with a Report of 18 Cases, Johns Hopkins Hosp. Repts. **16** 363, 1911.

# THE ORIGIN OF FIBROBLASTS WITHIN AN EXPERIMENTAL HEMATOMA<sup>\*</sup>

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The origin and interrelationship of the cells that comprise the connective tissue and the blood is a problem concerning which the opinions of competent investigators are at variance. Their conflicting interpretations, based on apparently sound experimental data, but data subject to personal analysis and error, confuse the literature. Excellent reviews of the current opinions of leading hematologists are available, and we shall not attempt to review such opinions except as they pertain to the subject under consideration.

That the clasmatoocytes, or tissue histiocytes, and fibroblasts originate from the leukocytes of the blood is not accepted by all hematologists. Sabin, Doan and Cunningham<sup>1</sup> did not accept the hematogenous origin of the clasmatoocyte. Maximow,<sup>2</sup> Lewis,<sup>3</sup> and others regarded the mononuclear leukocyte of the blood as the progenitor of most of the tissue macrophages. Recently, numerous studies have been published which attempt to establish the ability of the nongranular leukocyte to transform into other types of cells. Since the advent of tissue culture as a means for the growth and the direct observation of cells, studies on isolated blood have added greatly to our knowledge of the potentialities of certain of these blood cells. From cultures of leukemic blood, Awrowow and Timofejewskij<sup>4</sup> concluded that the lymphocytes are the stem cell from which the mononuclear leukocytes arise and that by successive division and differentiation the latter may be converted into the various other types of cells such as the macrophages, the giant cells, and even the spindle-shaped connective tissue cells. They do not use

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<sup>\*</sup> From the Division of Experimental Surgery and Pathology of The Mayo Foundation

1 Sabin, F R, Doan, C A, and Cunningham, R S. Discrimination of Two Types of Phagocytic Cells in the Connective Tissues by the Supravital Technique, *Contributions to Embryology* **15-16** 125, 1923-1925

2 Maximow, A. Experimentelle Untersuchungen uber entzundliche Neubildung von Bindegewebe, *Beitr z path Anat u z allg Pathol*, 1902, suppl 5, pp 1-262

3 Lewis, M R. The Formation of Macrophages, Epithelioid Cells and Giant Cells from Leucocytes in Incubated Blood, *Am J Path* **1** 91, 1925

4 Awrowow, P P, and Timofejewskij, A D. Kultivierungsversuche von leukamischem Blute, *Virchow's Arch f path Anat* **216** 184, 1914

the term fibroblast or clasmatocyte, although the cells they observed were probably of these types. Carrel and Ebeling<sup>5</sup> developed pure strains of the mononuclear leukocytes of the blood of adult chickens, these were kept viable for considerable periods. Cultures of pure monocytes were obtained, which differentiated into cells having the appearance of fibroblasts, although there was but slight tendency on their part to form tissues. The extent of this differentiation could be accentuated somewhat by the addition of small quantities of an embryonic extract. Lewis,<sup>3</sup> and Lewis and Lewis,<sup>6</sup> in studies of hanging drop preparations of either heart or peripheral blood of a number of vertebrates, concluded that macrophages, epithelioid cells and giant cells may arise from the blood monocytes, but that the granulocytes do not play a part in the formation of other types of cells. In these preparations they observed spindle-shaped, fibroblast-like cells, which they believed were merely elongate, multipolar macrophages, they did not find any evidence that true fibroblasts had developed from the monocytes. Fischer,<sup>7</sup> perhaps more than any other observer, showed a direct transformation of monocytes into connective tissue. Chick plasma containing leukocytes, together with a certain amount of embryonic extract and a fragment of muscle, was cultured and subcultured a number of times. In the fourth subculture only monocytes occurred, and some of these had become transformed into fibroblasts. In subsequent subcultures, the preparations resembled cultures of ordinary connective tissue, which later became more extensive. Accordingly, Fischer concluded that it is possible to obtain a strain of connective tissue cells from cellular elements taken directly from the blood of adult animals. Maximow<sup>8</sup> in studies on blood cultured with an extract of inflamed connective tissue from a rabbit, showed that the granulocytes degenerate within forty-eight hours but that the lymphocytes and the monocytes remain alive and soon differentiate into polyblasts. Even the lymphocytes hypertrophy and give rise to monocytes with typically kidney-shaped nuclei. Bloom<sup>9</sup> showed that the lymphocytes of the thoracic duct may transform into

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5 Carrel, Alexis, and Ebeling, A. H. Pure Cultures of Large Mononuclear Leucocytes, *J. Exper. Med.* **36** 365, 1922

6 Lewis, M. R., and Lewis, W. H. Transformation of Mononuclear Blood-Cells into Macrophages, Epithelioid Cells, and Giant Cells in Hanging-Drop Blood-Cultures from Lower Vertebrates, *Contributions to Embryology* **18** 95, 1926

7 Fischer, Albert. Sur la transformation in vitro des gros leucocytes mononucleaires en fibroblasts, *Compt. rend. Soc. de biol.* **92** 109, 1925

8 Maximow, A. Ueber die Entwicklungsfähigkeiten der Blutleukocyten und des Blutgefässendothels bei Entzündung und in Gewebekulturen, *Klin. Wchnschr.* **4** 1486, 1925

9 Bloom, William. Transformation of Lymphocytes of Thoracic Duct into Polyblasts (Macrophages) in Tissue Culture, *Proc. Soc. Exper. Biol. & Med.* **24** 567, 1926-1927

clasmatocytes, and Maximow<sup>10</sup> showed, in studies in vitro, that both lymphocytes and monocytes may transform into fibroblasts

This brief review of the literature seems to indicate that some opposition to the concept of a direct transformation is still encountered, for, according to certain investigators, only fibroblast-like cells, which were temporarily spindle-shaped, developed in the cultures of the blood monocytes. These soon reverted to the macrophage type.

We wish to present here the results of certain studies which lead us to conclude that both monocytes and clasmatocytes may differentiate into fibroblasts, points concerning which there is some question. Experimentally produced hematomas of varying consecutive durations provide a satisfactory means for the study of the series of changes which transpire in blood when isolated from its normal channels. Such areas of blood are walled off from the body tissues, and the conditions which obtain are not entirely unlike those attendant on tissue culture. Temperatures are maintained constant, and circulation of new blood to the region is cut off at least during the period of study. Tissue juices that perhaps abound may correspond, in part, to the embryonic extract added to the blood when cultured in vitro. Accordingly, we were of the opinion that successive stages of such experimental hematomas would reveal the relative potency of certain of the blood cells, that is, the possibility of progressive development that may abound in them. One must grant, always, that a study based on sections has its limitations, and that sections can never be as adequate a means for the determination of cell continuity as tissue cultures, which permit relatively uninterrupted observation of a given cell.

#### OBSERVATIONS

The subserous spaces in the walls of the stomach and cecum of rabbits were selected as the site of the hematomas to be experimentally produced. After an aseptic injection of small quantities of autogenous blood into these areas, the animals were killed at intervals of three, five, seven, eleven, twenty-one, thirty, forty-eight and seventy-two hours. The portion of the gastro-intestinal tract, including the site of the interjection, was excised and fixed in a 10 per cent solution of formaldehyde, sectioned and stained with hematoxylin and eosin.

In the early hematomas studied, those included in the three and five hour series, the erythrocytes were intact and occasional lymphocytes, monocytes and polymorphonuclear leukocytes were present as in normal blood. Changes in any of the cells were not visible at this time. In the seven hour hematoma, however, slight changes in the organization

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<sup>10</sup> Maximow, A. Development of Non-Granular Leucocytes (Lymphocytes and Monocytes) into Polyblasts (Macrophages) and Fibroblasts in Vitro, *Proc Soc Exper Biol & Med* **24** 570, 1926-1927

could be noted. The erythrocytes showed some signs of destruction, but most marked, probably, were the changes in the nuclei of the large monocytes. They had become more hyperchromatic, their color resembling somewhat that of the lymphocytes, and they had become slightly elongated, although still possessing their characteristic indented margin. Such changes are the first to be visible in these cells, which undergo extensive modification in later stages.

Early in the production of the hematomas the polymorphonuclear leukocytes showed signs of destruction, which is evidence that they do not play a part in the organization or transformation which ensues. The time and rate of their disappearance seem variable, for in certain stages of thirty hours' duration they were not identified, while in others they were recognized as late as seventy-two hours after the injection. This decomposition of the polymorphonuclear leukocytes has been shown to take place in tissue cultures as well. Carrel and Ebeling<sup>5</sup> noted the disappearance of both the granulocyte and the lymphocyte from their preparations, after the third or fourth subculture, and Maximow<sup>8</sup> showed that the granulocytes degenerate within forty-eight hours.

It seems evident from sections of hematomas of slightly longer duration that these cells, which rather rapidly increase in number and which possess a variety of shapes ranging from ameboid types with filiform or lobal pseudopodia to forms more distinctly spindle-shaped, are not derived from the tissue peripheral to the site of the hematoma. On the contrary, these cells are probably derivatives of the large monocytes, and possibly of the lymphocytes, which are normally within the injected blood. Evidence is not present that these cells have migrated from the body tissue into the blood. The number of cells within the center of the hematoma is even greater than the number in the periphery, and further, the central cells do not show greater differentiation than do those nearer the periphery, a condition which might ensue were these cells of extraneous origin.

In the hematomas of fourteen and twenty-one hours' duration certain of the cells show considerable differentiation. Most of the polymorphonuclear leukocytes have fragmented extensively, but the monocytes are more abundant and have given rise both to ameboid and to spindle-shaped cells, with somewhat elongated cytoplasmic bodies. In the thirty hour stages, the fragmented portions of the polymorphonuclear leukocytes have largely disappeared, and two rather definite types of cells are present. One of these is a large, oval cell with a single, slightly indented nucleus and clear, rather finely granular cytoplasm. This is unquestionably the blood monocyte, the clasmatocyte, or the phagocytic histiocyte of Aschoff. The other type of cell present in the thirty hour hematoma is markedly spindle-shaped, with a greatly compressed nucleus and with a cytoplasmic body now greatly attenuated,

reaching for a considerable distance among the erythrocytes. From its shape and general appearance this cell must be a fibroblast. As evidence of a peripheral origin for them is lacking, the two types of cells must be derived from the interjected blood and thus be of hematogenous origin.

In the forty-eight hour experiments these cells are further differentiated, and many of them contain numerous granules of pigment. This is particularly true of the large clasmotocytes, although the fibroblasts are frequently equally well distended with pigment (fig 1). As fibroblasts are normally but slightly phagocytic, it is not likely that these cells have ingested these foreign particles after becoming so attenuated.



Fig 1—A fibroblast and a group of macrophages with ingested material in a hematoma forty-eight hours old,  $\times 1,000$

It is more likely that the clasmotocytes which give rise to the fibroblasts had already become phagocytic before the transformation occurred. Besides these fibroblasts with inclusions of pigment, there are many others (figs 2 and 3) which are devoid of any such phagocytosed material. Some of these are equal in size to the pigmented cells, while others are much smaller. The large fibroblasts free of pigment are probably transformed monocytes which had not phagocytosed foreign particles, while the smaller fibroblasts may be of lymphocyte origin, a conclusion not entirely verified, although Maximow<sup>10</sup> demonstrated in tissue culture the transformation of the small lymphocytes into macrophages.





Fig 2—Fibroblasts with and without ingested material and a group of macrophages in a hematoma seventy-two hours old,  $\times 475$



Fig 3—A macrophage with packed particles and a fibroblast without packed particles in a hematoma seventy-two hours old,  $\times 1,000$

## COMMENT

These observations in the early stages of a series of hematomas, artificially produced, rather clearly demonstrate the ability of certain cytologic elements of the blood to differentiate progressively into other cells. This differentiation is restricted to the monocytes and lymphocytes, for the polymorphonuclear leukocytes degenerate within forty-eight to

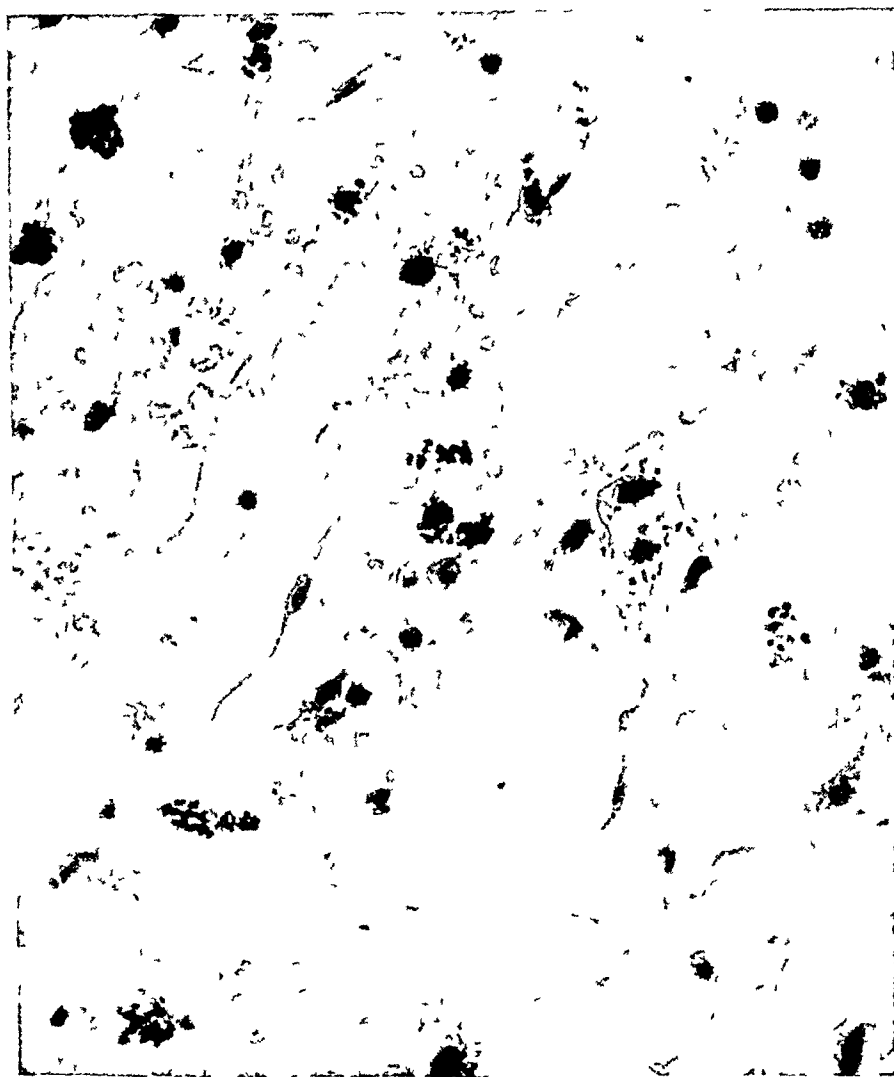


Fig 4—Fibroblasts with greatly attenuated processes with and without phagocytosed particles in a hematoma seventy-two hours old,  $\times 475$

seventy-two hours and their fragments are largely phagocytosed. The cell which becomes the most active and essentially the formative factor in the organization of the hematoma is the large blood monocyte. As early as from six to eight hours following the interjection of the blood into the subserous coat of the stomach the nuclei of certain of these monocytes have become more ovoid, and there is some tendency to a spindle-shaped form in the cell itself. Subsequent stages in the organiza-

tion of the hematoma show further differentiation of these cells, which results in the development of two entirely distinct types, identified as the clasmatocyte or blood histiocyte and the fibroblast. In hematomas of forty-eight, sixty and seventy-two hours' duration these two types are readily identified, and in the later stages their phagocytic activity is well marked. The large, round clasmatocytes are well distended with phagocytosed pigment, and the elongated fibers of the spindle-shaped fibroblasts contain many inclusions of pigment. Besides these pigment-containing fibroblasts, there are smaller fibroblasts without pigment but with processes nearly as elongated. The large fibroblasts, containing the granules of pigment, have arisen through a transformation of the clasmatocyte after phagocytic activity has begun. These smaller fibroblasts, on the other hand, have probably arisen in one of two ways: either as a transformation of the monocyte before phagocytosis had taken place or, as Maximow has shown, in tissue culture, directly from the larger lymphocytes. The fibroblasts which appear in these seventy-two hour hematomas are not fibroblast-like cells with only a temporary spindle form as some have described it, but rather show a definite course of progressive development from monocytes into connective tissue fibrils (fig. 4).

On the basis of these observations on a series of experimentally produced hematomas, we conclude that (1) the blood monocytes and the lymphocytes may differentiate into other histiocytic elements, (2) the monocytes may differentiate into clasmatocytes or directly into fibroblasts, (3) the clasmatocytes may further differentiate into fibroblasts and (4) the lymphocytes may also differentiate into fibroblasts.

# SPLENIC ATROPHY WITH CALCIUM AND IRON INCRUSTATIONS (NODULAR SPLENIC ATROPHY)

REPORT OF A CASE<sup>\*</sup>

G A BENNETT, M D

BOSTON

Nodular splenic atrophy has been only rarely recorded and is probably of infrequent occurrence. Hennings<sup>1</sup> and Goldberg<sup>2</sup> reported instances that were somewhat similar both grossly and microscopically. In the specimen to be described, as in those previously described, there was, in addition to a marked atrophy, an extensive deposition of iron pigment and lime salts.

## REPORT OF CASE

Because I was unable to determine any significant relationship between the small atrophic spleen and the patient's condition, I shall give only the briefest résumé of the clinical observations.

*History*—An unmarried negress, aged 20, entered the hospital complaining of pain in the legs, arms, back and neck. The illness had begun ten days before with a sore throat, headache and general malaise. On the day after admission, signs of pneumonia of the right lower lobe were made out. The clinical examination, including lumbar puncture, did not yield results of any significance, except a Wassermann reaction of one plus<sup>3</sup>.

*Necropsy*—A complete examination six hours after death revealed an early lobar pneumonia and extensive necrosis of the liver, but no lesions of special interest except in the spleen.

The spleen weighed 10 Gm and measured 4 by 27 by 15 cm in its greatest diameters. It retained much the contour of a normal spleen, and on cross section it was evenly triangular. On the anterior margin, however, was a small nodule 0.5 cm in diameter, which was less firm and retained more of the normal consistency and normal appearance of splenic tissue. The section revealed a dark slate colored surface containing strands of rather coarse fibrous connective tissue. One portion near the hilum gave a grating sensation when scraped with a knife. The splenic artery was much reduced in size, measuring on cross section approximately 2 mm in diameter, but there was no thrombosis or occlusion of either artery or vein.

Examination of the other organs, including the brain and spinal cord, did not reveal anything of importance. A noteworthy feature, however, was that

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<sup>\*</sup> From the Pathological Laboratory of the Peter Bent Brigham Hospital and Harvard University Medical School.

1 Hennings, K. *Virchows Arch f Path Anat* **259** 244, 1926

2 Goldberg, S E. *Proc New York Path Soc* **26** 141, 1926

3 Wassermann reactions in the Peter Bent Brigham Hospital are recorded as one plus and two plus.

nothing in the way of arteriosclerosis or atheroma was found in any of the arteries elsewhere in the body

*Microscopic Examination of the Spleen*—A small portion of the spleen was fixed in Zenker's solution, from which routine sections were made. The remainder of the material was fixed in formaldehyde, and this material was subsequently used for special stains, in both frozen and paraffin sections. The stains used were eosin methylene blue, hematoxylin and eosin, Roehl's hematoxylin method for staining calcium, von Kossa's and Klotz' silver method for staining calcium, ferrocyanide of potassium (Mallory) and Turnbull's blue for iron and Weigert's method for elastic tissue.

Each section represented a total cross section of the spleen. The general structural framework of the spleen was present, but the lymphoid element was



Fig 1—Cross sections of three portions of spleen showing marked atrophy with fibrosis and thickened walls of blood vessels,  $\times 14$

almost entirely gone. Malpighian corpuscles were not found. The splenic capsule was somewhat thickened and there was an unusual prominence of the trabeculae, with here and there circumscribed areas consisting of dense fibrous connective tissue. The wide trabeculations were closely applied to one another, there being only blood, pigment, small clumps of lymphocytes and a few polymorphonuclear leukocytes and endothelial cells in the intertrabecular spaces. The vascular sinuses, where seen, were engorged with blood, and in some instances there was extravasation of blood. The blood vessels were unusually prominent and showed considerable thickening of their walls. In most instances, the small and medium-sized vessels were patent, though occasional ones were thrombosed, and these, in a few instances, showed canalization.

A considerable amount of blue and bluish-black granular deposit was seen with ordinary stains in the thickened walls of the blood vessels and in the fibrous connective tissue of the trabeculae. This substance was undoubtedly calcium, as it stained intensely with the hematoxylin, and black with the silver nitrate methods. Tissues treated with mineral acids showed complete loss of this material. When acetic acid was added to small blocks of tissue, an effervescence was noted both grossly and microscopically. Frozen sections which had been previously treated with half concentrated solution of oxalic acid to remove the iron present, and then stained as were the other sections for a brief period with silver nitrate, showed a marked thickening of the elastic lamina of the blood vessel wall, which stained black and was somewhat granular. It seems

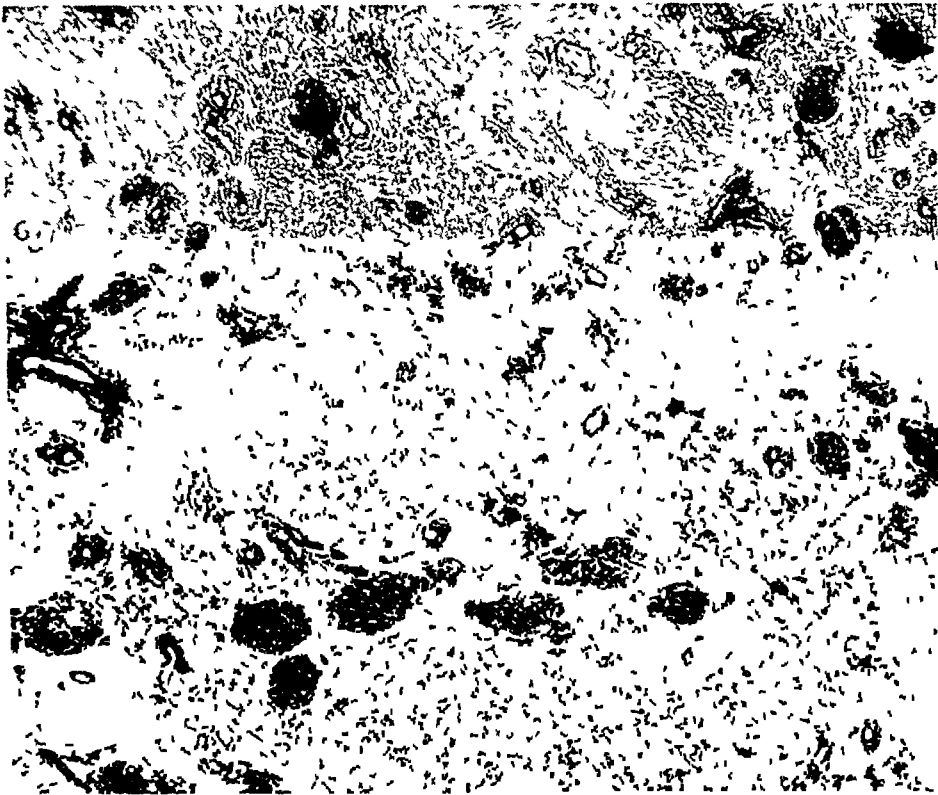


Fig 2—Section showing the iron and calcium deposited about blood vessels and in the fibrous and elastic tissues, stained with hematoxylin and eosin. Low power magnification.

likely from this staining reaction that the excess of lime was deposited in these laminae.

Scattered throughout the areas described was a striking amount of brownish-yellow material, which subsequently gave the characteristic iron reaction when stained by the methods mentioned. The iron could be seen both as finely divided granular particles and as an intensely blue staining material, which spread out diffusely through the connective tissue and the walls of the blood vessels. A small proportion stained as a precipitate in the pulp spaces, but, in general, it appeared to be intimately bound to the elastic and collagen structures.

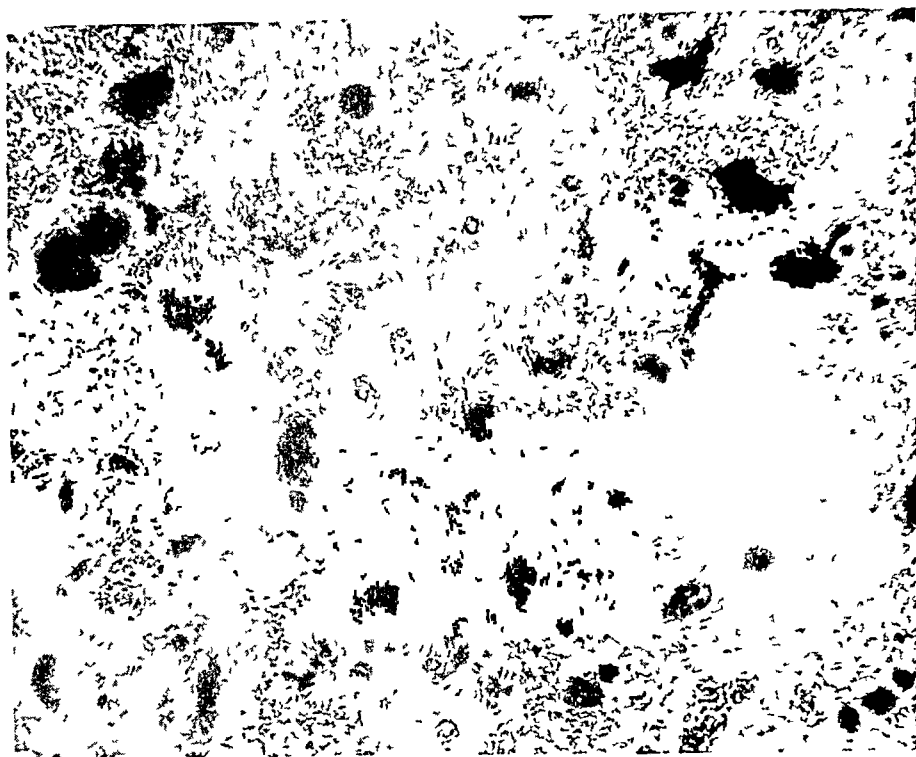


Fig 3—Frozen section showing the intensely staining material to be iron stained with ferrocyanide of potassium (Mallory) Low power magnification



Fig 4—Frozen section showing calcium in the walls of blood vessels and fibrous tissue, stained by von Kossa's silver method after removal of iron Medium power magnification

## REVIEW OF LITERATURE

Sprunt,<sup>4</sup> in studying incrustations of calcium and iron in the elastic tissue of the spleen and the liver, concluded that degenerated, and especially calcified, elastic tissue—even more than calcification in general—seemed to possess an affinity for iron salts. The incrustations of iron occurred principally in congested or hemorrhagic areas. The distribution of the iron and the calcium in the spleen which he described follows closely that in the one here reported, which likewise showed a predominance of the iron, and the presence of iron without calcium in some areas. Watts<sup>5</sup> demonstrated the association of these two substances in the choroid plexus and found that certain features suggested strongly that calcification follows thrombosis of the vascular supply to the plexus. Ehrlich<sup>6</sup> reported that elastic fibers in the neigh-



Fig 5—Frozen section stained with silver nitrate, showing calcium deposited in the elastic lamina of arterial walls. Medium power magnification.

borhood of scars or infarctions have a tendency to absorb iron. He believed that the deposit of iron precedes that of calcium and found them both present in the elastic fibers and scars of splenic infarctions. Gierke<sup>7</sup> called attention to the physiologic association of calcium and iron in the fetus in which the entire skeleton contains iron as far as it has been calcified, with an excess at the points of active ossification. Although the reports of incrustations of calcium and iron indicate that they are most numerous in the spleen, a similar association of the two substances has been described as occurring also in the elastic fibers of

4 Sprunt, J. *Exper Med* **45** 59, 1911.

5 Watts, J. *Deposition of Calcium Salts in Areas of Calcification*, *Arch Surg* **15** 89 (July) 1927.

6 Ehrlich, S. *Centralbl f allg Path u path Anat* **17** 177, 1906.

7 Gierke. *Virchows Arch f path Anat* **167** 318, 1902.



lungs which were the seat of chronic passive congestion (Bittrolff<sup>8</sup> and Kockel<sup>9</sup>) In searching for a suitable explanation of the pathologic deposition of calcium, one must first consider its possible source Holt, LeMer and Chown<sup>10</sup> believed that calcium is transported as a readily soluble acid carbonate and acid phosphate, which may be converted into neutral salt by the loss of carbon-dioxide Watts,<sup>5</sup> in utilizing this information, pointed out that "in places of low grade activity, such as necrotic areas, regions of fibrosis, and thrombosed vessels, there is probably little carbon-dioxide Any fluids entering these areas will have their concentration of carbon-dioxide reduced and their calcium salts will precipitate" Hueck<sup>11</sup> claimed that the presence of iron in areas of calcification may be due to impurities of iron containing fixatives or to the solution of hemoglobin in fixatives which would allow its iron constituents to be deposited in calcified areas These factors would hardly explain the entire picture as seen in the spleen in question and in those described by others, in which iron is deposited in excess of the calcium and in areas in which calcium cannot be demonstrated Klotz<sup>12</sup> observed in arterial lesions that many calcified elastic fibers are seen in which iron cannot be demonstrated On the other hand, iron-containing elastic elements were not found in the absence of calcification Hennings'<sup>1</sup> report would indicate that the condition found in these spleens is produced by an increased destruction of red corpuscles after hemorrhage with deposition of hemosiderin and a peculiar disintegration of the elastic collagen material of the sclerotic wall of the blood vessel Goldberg<sup>2</sup> pointed out that the excessive destruction of the red corpuscles may have been due to a toxic process or an infectious process, and that necrosis of the splenic tissue may have caused the precipitation of the iron pigment and the lime around the sclerotic areas, which had subsequently been replaced by a formation of connective tissue

## COMMENT

The interesting features of the spleen described in this paper are its extreme smallness, and the presence of iron and calcium incrustations in the walls of the blood vessels and in fibrous and elastic tissues of the trabeculae Calcium deposit does not seem to have specificity for spleens of small size, and it has been found in various lesions of spleens as well as in those of other organs Kaufmann<sup>13</sup> made note of the

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8 Bittrolff Beitr z path Anat u allg Path **49** 213, 1910

9 Kockel Deutsches Arch f klin Med **64** 332, 1899

10 Holt, L E, LeMer, V K, and Chown, H B J Biol Chem **64** 509, 1925

11 Hueck Centralbl f allg Path u path Anat **19** 774, 1908

12 Klotz, O Bull Johns Hopkins Hosp **27** 363, 1916

13 Kaufmann Spezielle pathologische Anatomie, ed 8, Berlin and Leipzig, W de Gruyter & Company, 1928, vol 1, p 184

cases of two aged women in which the spleens, weighing 19 and 10 Gm, respectively, revealed that the splenic pulp had largely disappeared and that the blood vessels and trabeculae had become correspondingly more prominent. In each instance, a brown, amorphous pigment was noted but apparently not identified. The "speckled spleen" of Feitis, recently reviewed by Hosoi,<sup>14</sup> does not seem to bear any definite relationship to the specimen under discussion, it is conceivable, however, that the necrotic areas of the "speckled spleen," with subsequent fibrosis, may terminate in a condition of nodular splenic atrophy. In the present case lesions of a similar nature in other organs could not be found, nor was there evidence of similar changes in the blood vessels elsewhere in the body. After consideration of the evidence at hand, it seems that because of iron in isolated fibers and in areas of considerable size without the presence of calcium the iron was of primary importance. It also seems that there was some etiologic factor, either in hemorrhage or in necrosis, or possibly in both, to cause the deposition of such a large amount of iron. While Goldberg's<sup>2</sup> case and the present one apparently represent the same pathologic process, there is one remarkable difference in that the former showed a nodular surface while the latter presented a surface that was smooth. It is interesting that both cases occurred in young negroes whose blood gave positive reactions in Wassermann tests.

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14 Hosoi, K. Multiple Necrosis of the Spleen with Special Reference to the "Speckled Spleen" of Feitis, *Arch Path* 6:26 (July) 1928.

# OBSERVATIONS ON RETICULO-ENDOTHELIAL CELLS IN SEPTIC JAUNDICE

IRVING SHERMAN, M D

BROOKLYN

A male child, 11 days old, developed frequent watery stools three days before admission to the hospital. On the following day the child became jaundiced, and twenty-four hours later a small, red spot appeared in front of the left ear. The redness spread down over the shoulder, the respiration became labored and the child cried a great deal when handled.

## REPORT OF CASE

*History*—The infant was well nourished, deeply icteric and acutely ill. The temperature was 101 F, respirations, 40 and pulse rate, 140. The lids were closed, and somewhat edematous. The lobe of the left ear was swollen, and the area around the lobe was red and puffy. The skin back of the neck was red, and there was a definite line of demarcation between this area and the rest of the skin. The heart and the lungs were normal. The liver was palpable one and a half fingerbreadths below the free costal margin. The spleen was hard, and it was felt one fingerbreadth below the free border. The urine was normal. The blood count showed 1,860,000 red blood cells, 40 per cent hemoglobin, and 5,500 white blood cells, of which 44 per cent were polymorphonuclears and 56 per cent lymphocytes. The blood culture showed 300 colonies of *Streptococcus hemolyticus* in 1 cc of blood. On admission, the child had been given 2,000 units of erysipelas antitoxin. Death took place after twenty-four hours.

*Autopsy*—The lungs were filled with air, except in the posterior part of the right upper lobe. In this region there was a reddish-brown, soft area, about 3 inches (7.6 cm) in diameter, which did not contain air. The same condition was found in the middle lobe of the left lung posteriorly. The heart was of medium size, and its muscle was firm. The valves were thin and smooth. The intima of the aorta was smooth. The spleen was enlarged, reddish and hard, the capsule tense, the pulp was dark red, and the trabeculae and follicles were not clearly visible. The liver was of average size, and was yellowish brown. Its structure was fairly well maintained. The gallbladder was filled with a yellowish-green bile, and the bile ducts were patent. The kidneys were of average size, the capsule stripped off readily, the surface was smooth and the structure was well maintained. The diagnosis was erysipelas, jaundice, septicemia and hypostasis of the lungs.

Microscopic examinations were made of the liver, spleen, bone marrow and suprarenal glands. On low power magnification, the structure of the liver seemed to be but slightly altered. The intertrabecular capillaries were wide and filled with some amorphous substance, which stained faintly. All the liver cells proper stained well. The veins were wide and contained much blood. High power

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From the Department of Laboratories, United Israel Zion Hospital

examination showed that the wide capillaries contained hardly any red blood cells. They were blocked by the enormously swollen Kupffer cells. Some of the latter were necrotic, the nuclei did not stain, and the cytoplasm was broken up. In the majority of the cells, however, the nuclei were well maintained, whereas the cytoplasm was vacuolated. Almost every cell contained a large number of bacteria which proved to be gram-positive streptococci, forming long chains (fig 1). A few cocci were visible outside the cells, too, but their number was insignificant as compared with the large number of cocci taken up by the Kupffer cells.

There was some coagulated albuminous substance in the sinuses, particularly where the swollen Kupffer cells seemed to disintegrate.

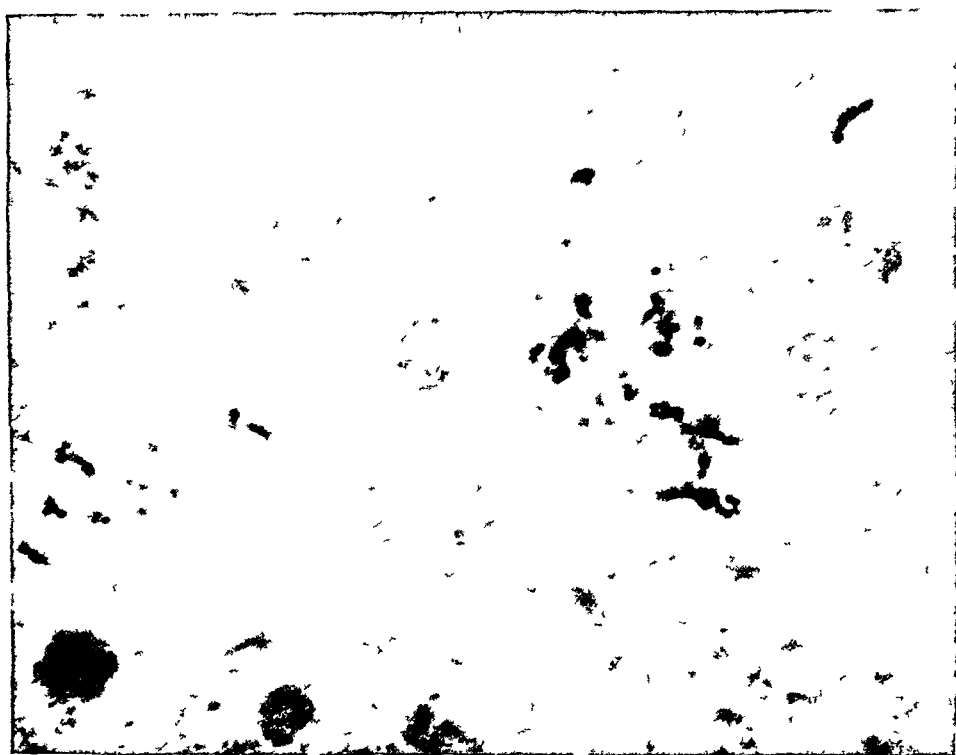


Fig 1—Phagocytosed streptococci in swollen Kupffer cells. Gram stain. Leitz apochr. Oil immersion. Aperture, 2 mm. Periplane eyepiece no 10.

But little bile pigment was visible in the liver. Most of this pigment occurred in the form of large droplets, almost the size of an erythrocyte. The droplets were found in small bile ducts.

Sections impregnated with silver after Otani's method showed the normal outline of the intracellular bile capillaries. There was no dilatation or rupture of the wall. Bile pigment was not present in these capillaries. This contrasted significantly with the bile casts which were found in some of the small bile ducts. The reticulum fibrils which lined the hepatic sinuses were poorly maintained, and apparently broken up in many places.

The most remarkable observation in the spleen under low power magnification was the scarcity and small size of the lymph follicles which consisted merely of an aggregation of small lymphocytes around little arteries. Secondary follicles were not visible. The pulp was engorged, and its cells appeared to be discrete, probably on account of the poor staining of the reticulum cell nuclei.

High power magnification showed that many of the sinus endothelial cells and also all the reticulum cells were necrotic. Some shadowy outlines of the nuclei were occasionally still visible. Other cells had completely disappeared. Many of the reticulum cells which still survived were swollen and contained a large amount of streptococci phagocytosed (fig 2). There were also large clusters of streptococci outside the cells, but it seems that these clusters were originally intracellular and became free after the phagocytic cell had disintegrated.

There was a large amount of yellowish or greenish-yellow pigment in the spleen. The pigment was irregularly granular, or crystalline. Pigment also appeared in the form of large, round droplets similar to those described in the liver. A positive iron reaction was obtained on almost the whole pigment.

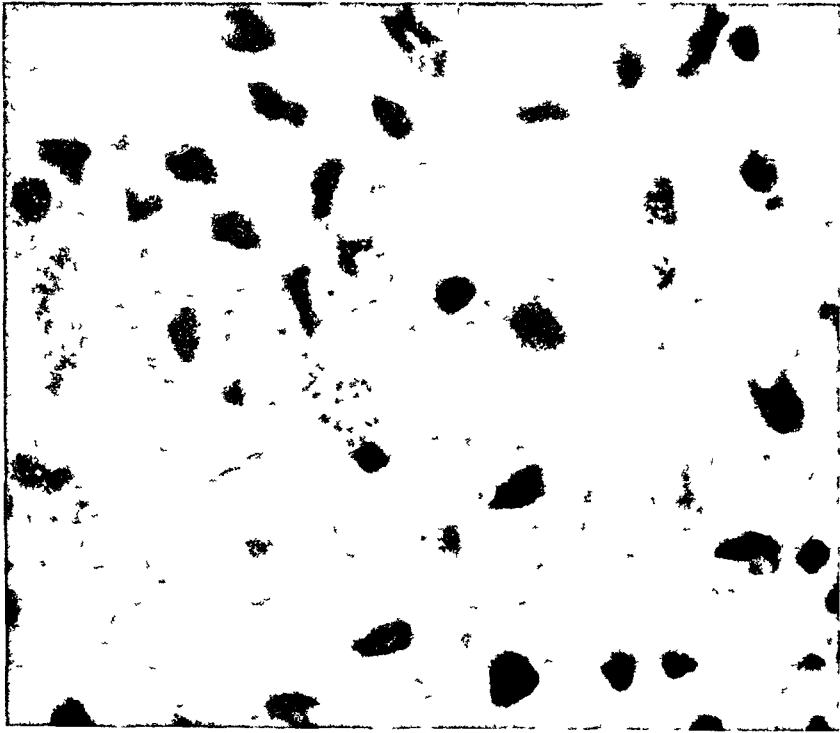


Fig 2—Phagocytosed streptococci in splenic reticulum cell. Hematoxylin-eosin. Leitz apochr. Oil immersion. Aperture, 2 mm. Periplane eyepiece no 10.

The bone marrow was cellular, and there were many myelocytes particularly eosinophil in type. Other cells included mature erythrocytes, erythroblasts, lymphocytes, myeloblasts, giant cells and reticulum cells. The reticulum cells were unusually large, apparently swollen, and vacuolated. The nuclei of some of these cells were pale or did not stain. Some of the cells contained streptococci, but there were also many cocci in the meshes of the reticulum. It was noteworthy that the extracellular cocci were found in areas in which the cell nuclei did not stain any more as evidence of necrosis.

Physiologic involution of the suprarenal cortex was not completed. The medulla was scanty, its cells seemed well maintained. The cortical tissue was edematous, and the capillaries were unusually wide. The sinus endothelial cells were swollen and resembled the Kupffer cells, although they were not as bulky.

There were vacuoles in the cytoplasm, and most of the cells contained a number of streptococci. Some of the endothelial cells were seen to break up. This began with granular disintegration of the cytoplasm, whereas the nuclei faded only later (fig 3).

#### COMMENT

The most remarkable observation in this case of overwhelming streptococcal infection was the enormous phagocytic activity of certain types of cells. These phagocytes included the Kupffer cells, the cells of the capillary endothelium of the suprarenals and the reticulum cells.

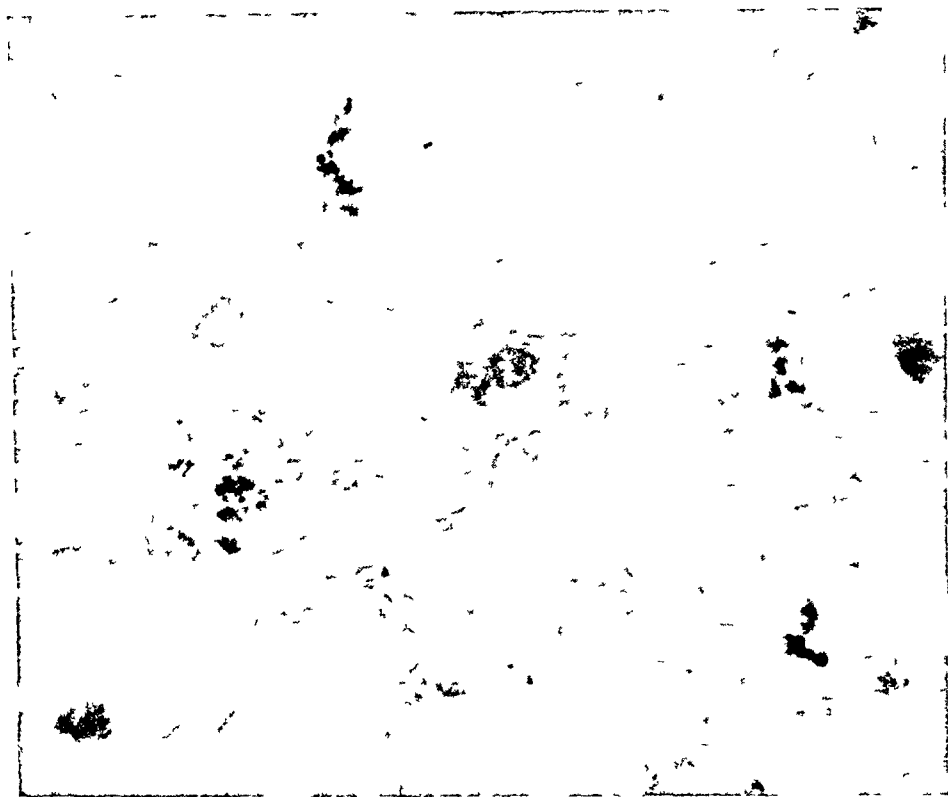


Fig 3—Phagocytosed streptococci in swollen endothelial cells, reticular zone of the suprarenal cortex. Gram stain. Leitz apochr. Oil immersion. Aperture, 2 mm. Periplane eyepiece no. 10.

of the bone marrow and the spleen. This observation is noteworthy for the following reasons: 1. Phagocytosis was not incidental with these cells, as, particularly in the liver, almost all the Kupffer cells participated. 2. The phagocytic activity seemed to be specific, as other capillary endothelium, even that of the splenic sinuses, did not share in the ingestion of the cocci.

It therefore seems that, in the case reported here, the aforementioned phagocytic cells represent a functional entity which does not correspond with the general conception of the reticulo-endothelial system.

This observation is supported by other features which indicate that the Kupffer cells and reticulum cells are capable of storing electively certain substances which are not taken up by the ordinary endothelium, or by that of the splenic sinuses. Reference is made to Gaucher's disease, in which leucasin is stored electively by the same cells which are found to phagocytose streptococci in the case reported.

The failure of the splenic sinus endothelium to participate in phagocytosis is more noteworthy because the cells are known to be markedly affected in acute infectious changes of the spleen (Goldzieher<sup>1</sup>). They are supposed to participate in the immunologic processes of defense. Furthermore, these cells are known to phagocytose and store other material, such as fat, pigment granules and cells, especially erythrocytes.

It is important to dwell on the incongruity of the general phagocytic and storing properties of the sinus endothelia and their failure to phagocytose or store under certain pathologic conditions in which the rest of the reticulo-endothelial system is highly active. An explanation of this fact is not available, yet it seems worth while to point to the experimental results showing that storage of fat can be greatly enhanced in the reticulo-endothelial system by the injection of hormones (Goldzieher and Hirschorn<sup>2</sup>), whereas the sinus endothelia again appear not to be affected by such stimulation.

Another point of interest is the relationship of the reticulo-endothelial involvement to jaundice. Minute examination of the liver did not reveal any evidence of obstruction of bile ducts, and examination of the intracellular bile capillaries proved that a retention of bile had not taken place within the liver cells.

Thus, both obstructive and pleiochrome jaundice are eliminated from consideration. In typical cases of hemolytic jaundice, one expects to find erythrophagocytosis. This was not seen in the present case. It seems, therefore, that the erythrocytes dissolved in the circulation, because of the effect of streptococcal toxins, and material for the formation of bilirubin was available in excess. The elimination of the bilirubin was interfered with somewhere, and it seems from what has been said before that the obstacle was encountered prior to the entrance of bilirubin into the liver cells. The liver cells proper could hardly be held responsible, as there was not any morphologic evidence of damage to the liver cells. On the other hand, the general and severe alteration of the Kupffer cells would indicate that the function of these cells in the elimination of bilirubin was severely interfered with.

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1 Goldzieher, M. A. The Structure of Infectious Splenic Swelling, *Arch Path* **3** 42 (Jan.) 1927.

2 Goldzieher, M. A., and Hirschorn, L. The Reticulo-Endothelial System III. The Influence of Hormones, *Arch Path* **4** 958 (Dec.) 1927.

It is not admissible nor intended to draw far-reaching conclusions from a single observation, nevertheless, this case seems to support the view that the liver cell is not the only factor in the formation of bilirubin, and that the Kupffer cells are actively engaged in the elimination of the bilirubin which is produced in other parts of the body. The Kupffer cells are instrumental in passing over bilirubin to the liver cells for further working up and elimination. In other words, this observation would support the view of Mann, Magath and Bollman,<sup>3</sup> about the formation of bilirubin outside of the liver, and would be against the contention of Melchior, Rosenthal and Licht,<sup>4</sup> that all other sources of possible formation of bilirubin outside of the liver are negligible.

#### SUMMARY

Excessive phagocytosis of streptococci was observed in a case of erysipelas with streptococcal septicemia. Kupffer cells, capillary endothelial cells of the suprarenal glands and reticulum cells of the spleen and the bone marrow participated electively in the phagocytosis. In the absence of any obstruction of the bile ducts, as well as of lesions in the liver cells, the jaundice was thought to have been caused by severe impairment of the Kupffer cells.

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<sup>3</sup> Mann, Magath and Bollman. *Am J Physiol* **69** 393, 1924.

<sup>4</sup> Melchior, E., Rosenthal, F., and Licht, H. *Klin Wchnschr* **5** 537, 1926.



# HISTOCHEMICAL EVIDENCE CONCERNING THE SITE OF THE FORMATION OF BILE PIGMENT<sup>1</sup>

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The disproportionate attention given to bilirubin, which is but one of the several important constituents of bile, is no doubt due to its striking properties of color, particularly as exhibited when this pigment is retained in the body, causing the clinical condition of jaundice. Added interest in bile pigment has resulted from the knowledge, beginning with the discovery of Virchow<sup>1</sup> in 1847 that a pigment resembling bilirubin is found in old extravasations of blood, that the pigment in the red cells of the blood is the chief if not the only source of bilirubin.

From earliest times, the association of the liver with bile has quite naturally led to the belief that the liver manufactured the various constituents of the bile and particularly the obvious biliary pigment. Occasionally, among the older writers, there was a dissenter. Morgagni,<sup>2</sup> in 1760, taught that the liver merely excretes the bile brought to it, already formed, by the blood. This view, however, did not receive serious study and investigation until the latter part of the nineteenth century. At this time, the status of the hepatic cell as the normal manufacturer of biliary pigment was scarcely questioned. Since then the pendulum of thought has swung to a position where it is debated whether or not the liver cell does more than merely excrete the pigment.

Virchow<sup>1</sup> failed to establish that the pigment in the old extravasations of blood was identical with bilirubin, and, to differentiate it, he gave it the name of "hematoidin." This unfortunate omission in his otherwise great discovery added confusion to the subject of pigmentary metabolism and delayed the pursuit of a clue that later gave the important additional information that extrahepatic formation of bilirubin is a fact. Rich and Bumstead,<sup>3</sup> in 1925, finally settled the lengthy controversy by subjecting "hematoidin" obtained from old hemorrhages to a series of twenty-six physical and chemical tests and reactions that are well established as characteristic of bilirubin, and in every instance "hematoidin" reacted precisely as did a control of pure bilirubin.

In 1886, Minkowski and Naunyn<sup>4</sup> appeared to have offered the final answer to the question of the site of the formation of the biliary pig-

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1 Virchow, R. Die pathologischen Pigmente, Arch f path Anat **1** 379, 1847.

2 Morgagni. De sedibus et causis morborum, epist 36, art 9.

3 Rich, A. R., and Bumstead, J. H. On the Identity of Hematoidin and Bilirubin, Bull Johns Hopkins Hosp **36** 225, 1925.

4 Minkowski, O., and Naunyn, B. Ueber den Icterus durch Polycholie und die Vorgange in der Leber bei demselben, Arch f exper Path u Pharmacol **21** 1, 1886.

ment They found that the intravascular hemolysis produced by arseniureted hydrogen in normal ducks and geese is regularly followed by intense jaundice, but that jaundice did not appear after such hemolysis in ducks and geese that had had their livers removed They concluded that the liver is the site of the origin of the biliary pigment, and the principles "without the liver no formation of bile pigment" and "without the liver no jaundice" were generally established

In 1903, Gilbert, Herscher and Posternak<sup>5</sup> disturbed the security of the status of the hepatic cell by reporting that normal human serum contains bile pigment This removed the important contention that bilirubin could not be formed outside the liver because biliary pigment could not be found in the circulating blood, not even in the portal vein Ten years later, van den Bergh and Snapper<sup>6</sup> applied Ehrlich's diazo-reaction to the quantitative study of bilirubin in the blood, thereby placing an extremely sensitive and delicate test in the hands of investigators It has been repeatedly confirmed that bilirubin is present in human plasma and that it belongs to the group of "threshold substances" for the kidney and also for the liver

In 1913, McNee<sup>7</sup> repeated the experiments in the dehepatization of ducks and geese that Minkowski and Naumyn had performed twenty-seven years previously and confirmed their observations But he interpreted his results far differently He concluded that the hepatic cells were not responsible for the production of the biliary pigment, but that the important agents were the Kupffer cells He concluded, and later Kyes<sup>8</sup> confirmed his conclusions, that the biliary pigment is formed in the cells of the reticulo-endothelial system described by Aschoff,<sup>9</sup> the Kupffer cells being a part of that system and a particularly important part in ducks and geese because of their small spleens and small amount of bone marrow

In that same year, Whipple and Hooper<sup>10</sup> attempted to exclude the liver from the circulation and found biliary pigment being formed rapidly in the blood stream following injections of hemoglobin Rich<sup>11</sup>

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5 Gilbert, Herscher, and Posternak Sur la reaction de Gmelin dans les milieux albumineux, *Compt rend Soc de biol* **55** 530, 1903

6 van den Bergh, A A H, and Snapper Die Farbstoffe des Blutserums, *Deutsches Arch f klin Med* **110** 540, 1913

7 McNee, J W Experiments on Haemolytic Icterus, *J Path & Bact* **18** 325, 1913-1914

8 Kyes The Physiological Destruction of Erythrocytes in Birds, *Internat Monatschr f Anat u Physiol* **21** 542, 1915-1918

9 Aschoff, Ludwig Lectures on Pathology, New York, Paul B Hoeber, 1924

10 Whipple, G H, and Hooper, C W Icterus A Rapid Change of Hemoglobin to Bile Pigment in the Circulation Outside the Liver, *J Exper Med* **17** 593, 1913

11 Rich, A R Experimental Studies Concerning the Site of Origin of Bilirubin, *Bull Johns Hopkins Hosp* **34** 321, 1923

ten years later repeated these experiments, the conclusions of which had gained somewhat general acceptance, and was unable to confirm the results. He ascribed the difference in results to the variation in the completeness of the exclusion of the liver from circulation. He proved, by using Whipple and Hooper's technic, that the circulation of the liver was not completely excluded, and that therefore his work did not warrant the conclusions concerning the part the liver plays in the formation of bilirubin.

Mann, Bollman and Magath,<sup>12</sup> using totally dehepatized dogs, made the important contribution that bile pigment can be formed and appears in the plasma entirely independent of any action of the liver. Rich<sup>13</sup> confirmed this observation in a series of experiments in which he removed all the intra-abdominal viscera. Bickel<sup>14</sup> and Makino,<sup>15</sup> employing the method of removal described by Mann,<sup>16</sup> also noted the development of jaundice in the totally dehepatized animals. It is, therefore, well established that extrahepatic formation of bile pigment is a fact.

Evidence has not been presented that bile pigment can be formed by any cells other than those of the "reticulo-endothelial system." These cells are found particularly in the liver as Kupfer cells, and in the spleen and bone marrow as reticulo-endothelial cells, and anywhere in the body as large wandering phagocytes. Lepehne,<sup>17</sup> seeking to establish their importance, attempted to block this system by injecting collargol and other substances. There was some temporary success in preventing the formation of biliary pigment, but the results were inconclusive, it being apparently difficult to block this system completely. Rich and Rienhoff,<sup>18</sup> van den Bergh and Snapper<sup>19</sup> and Kaznelson<sup>20</sup> found that blood

12 Mann, F. C., Bollman, J. L., and Magath, T. B. Formation of Bile Pigment After Total Removal of the Liver, *Am J Physiol* **69** 393, 1924.

13 Rich, A. R. On the Extrahepatic Formation of Bile Pigment, *Bull Johns Hopkins Hosp* **36** 233, 1925.

14 Bickel, A. Leberextirpation und Avitaminose in ihren Beziehungen zum Zuckstoffwechsel, *Deutsche med Wchnschr* **39** 140, 1923.

15 Makino, J. Beitrage zur Frage der anhepatocellularen Gallenfarbstoffbildung, *Beitr z path Anat u z allg Path* **72** 808, 1924.

16 Mann, F. C. Studies on the Physiology of the Liver. 1. Technic and General Effects of Removal, *Am J M Sc* **161** 37-42, 1921.

17 Lepehne, George, Milz, and Leber. Ein Beitrag zur Frage des hamatogenen Ikterus, zum Hamoglobin und Eisenstoffwechsel, *Beitr z path Anat u z allg Path* **64** 55, 1918, Untersuchungen uber Gallenfarbstoff im Blutserum des Menschen, *Deutsches Arch f klin Med* **132** 96, 1920, Weitere Untersuchungen uber Gallenfarbstoff im Blutserum des Menschen, *ibid* **135** 79, 1925.

18 Rich, A. R., and Rienhoff. The Bile Pigment Content of the Splenic Vein, *Bull Johns Hopkins Hosp* **36** 431, 1925.

19 van den Bergh, A. A. H., and Snapper. Ueber anhepatische Gallenfarbstoffbildung, *Berl klin Wchnschr* **52** 1081, 1915.

20 Kaznelson. Beitrag zur Entstehung des hamolytischen Ikterus, *Wien Arch f inn Med* **1** 563, 1920.

from the splenic vein, in certain conditions, contains much more bilirubin than blood from the splenic artery or other veins

With the reticulo-endothelial system fairly well established as a definite extrahepatic source of bilirubin, the controversy at present is over the relative rôles that the hepatic cells and the reticulo-endothelial cells of Aschoff play in the normal production of the biliary pigment. Lubarsch<sup>21</sup> expressed the belief that beyond all doubt the hepatic cell can produce biliary pigment. He based his belief to some extent on the finding of bilirubin within the cells of metastases of primary carcinoma of the liver. Rosenthal and Melchior<sup>22</sup> urged that, the reticulo-endothelial cells being active phagocytes, the finding of biliary pigment and pigment containing iron by the side of hemoglobin indicates that all three substances could have been phagocytosed, so that catabolism from hemoglobin within the cell is not necessarily implied.

The view that the reticulo-endothelial cells are the site of origin of the biliary pigment is held at present, especially, by Aschoff,<sup>23</sup> Lepehne,<sup>17</sup> Eppinger,<sup>24</sup> and McNee.<sup>25</sup> Mann<sup>26</sup> thought that the liver need not be considered of importance as far as the formation of the biliary pigment is concerned. Rich<sup>27</sup> stated that we are unable to speak with certainty about the normal site of the formation of the biliary pigment. Nevertheless he plainly stated that proof of the formation of the biliary pigment by the epithelial cells of the liver, under any circumstances, is lacking, and that the pigment can be formed independently of the activity of the hepatic cells. He did not consider it proved that cells of the reticulo-endothelial type can form the biliary pigment, but stated that evidence for its formation by any other type of cell or for its formation extracellularly by enzyme action, is lacking. He cited the work of Tarchanoff<sup>28</sup> and others to show that the hepatic cell possesses a remarkable power of taking up biliary pigment from the blood stream, and thereby invalidates the argument of Lubarsch.

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21 Lubarsch. Zur Entstehung der Gelbsucht, Berl klin Wchnschr **58** 757, 1921

22 Rosenthal and Melchior. Untersuchungen über die Topik der Gallenfarbstoffbildung, Arch f exper Path u Pharmacol **38** 421, 1922

23 Aschoff, L. Ueber den Ort der Gallenfarbstoffbildung, Klin Wchnschr **3** 961, 1924

24 Eppinger, Hans. Die Hepato-Lienal Erkrankungen, Berlin, Julius Springer, 1920, p. 544

25 McNee, J. W. Jaundice, a Review of Recent Work, Quart J Med **16** 390, 1922-1923

26 Mann, F. C. The Site of Formation and Source of Bilirubin, Arch Path **2** 516 (Oct) 1926

27 Rich, A. R. The Formation of Bile Pigment, Physiol Rev **5** 182, 1925

28 Tarchanoff. Ueber die Bildung von Gallenpigment aus Blutfarbstoff in Thierkorper, Arch f d ges Physiol **9** 329, 1874

Concise resumé of the voluminous literature on the various phases of this subject can be found in excellent reviews by Rich,<sup>27</sup> Mann,<sup>28</sup> and Whipple<sup>29</sup>

In reviewing the literature we felt that inadequate attention had been paid to histochemical evidence. Certain histochemical phases had been well covered, as in the work of Langhans,<sup>30</sup> who in 1870 studied experimental extravasations of blood and accurately observed the breaking down of hemoglobin into "hematoidin" by the large wandering phagocytes. Lowit<sup>31</sup> in 1889, working on the livers of normal frogs and of frogs in which experimental hemolysis had been produced, concluded that under both normal and pathologic conditions biliary pigment could be formed outside the epithelial hepatic cells within the phagocytic cells of the liver, spleen, bone marrow and circulating blood. His paper appeared shortly after the famous publication of Minkowski and Naunyn,<sup>4</sup> so that, since he admitted freely the formation of biliary pigment by the hepatic cells the significance of his paper was lost. Rich<sup>32</sup> saw red cells of the blood, in a culture from tissue, under the microscope, phagocytosed by the mesenchymal cells and transformed into bilirubin, leaving a residue containing iron. Others accurately described the breakdown of hemoglobin in the reticulo-endothelial cells in various animals and in man. But no one with whose work I am familiar, attempted in any considerable number of cases to study the histochemical evidence, using human material found at autopsy. Certain scattered observations led me to believe that such a study might throw some light on the controversy as between the reticulo-endothelial and the hepatic cells.

In various pathologic conditions associated with anemia one commonly finds bilirubin and a granular substance containing iron, called hemosiderin, side by side in the hepatic cells. Moreover, this hemosiderin is most obvious in the cells around the portal vein, while the bilirubin is most marked around the central vein. Are these pigments evidence of a transformation, within the hepatic cells, of hemosiderin into bilirubin? Are these granules containing iron merely residues after the transformation into bilirubin has taken place? Or are they stored iron, or iron in the process of excretion, or iron being built up into hemoglobin to be utilized by new red cells of the blood? And can these pigments found together in the hepatic cells be interpreted in the same way as when found together in reticulo-endothelial cells?

29 Whipple, G. H. The Origin and Significance of the Constituents of Bile, *Physiol Rev* **2** 440, 1922

30 Langhans. Beobachtungen über Resorption der Extravasate und Pigmentbildung in denselben, *Virchows Arch f path Anat* **49** 66, 1870

31 Lowit. Beiträge zur Lehre vom Icterus, *Beitr z path Anat u z allg Pathol* **4** 225, 1889

32 Rich, A. R. The Formation of Bile Pigment from Haemoglobin in Tissue Cultures, *Bull Johns Hopkins Hosp* **35** 415, 1924

## PROCEDURE

From seventy-one subjects who came to autopsy selected at random, blocks of tissue were taken usually from the liver and the spleen and occasionally from the kidneys, bone marrow, lungs, suprarenal gland, pancreas and lymph nodes. Some tissues were taken from material in stock, fixed in the Zenker-formaldehyde solution. The unfixed tissues were run through alcohol and cedar oil. The Zenker-fixed tissues were run through iodine-in-alcohol and mercuric-alcohol to remove the precipitate. Thin paraffin sections were stained with potassium ferrocyanide with use (after some experimentation with other stains) of Maude Abbott's high temperature modification of Mallory's technic<sup>33</sup>. The sections were examined for evidence of intracellular and extracellular, diffuse or granular material containing iron and brown pigment not containing iron, resembling bilirubin.

To study the effect of an increased supply of hemoglobin available for catabolism into biliary pigment, varying doses of serum from hemolyzed rabbits' blood were injected intravenously into a series of seven rabbits, various intervals of time being allowed to elapse between injections and between the final injections and death. Two rabbits were used as controls. One rabbit was killed by the intravenous injections of antihemolytic serum. One dog that died a few hours after being overtransfused, was studied. As these procedures did not yield additional information, the work will not be detailed.

## OBSERVATIONS

*Spleen*—Pigment was not discoverable in the organ in some cases, particularly in the spleens of young persons. Rather often there was found only a small amount of hemosiderin, but in the majority of cases a moderate amount, and in several cases of various types of anemia there was a marked amount of this pigment. Bilirubin was satisfactorily identified in small amounts in some instances.

Pigment was not found in the splenic arteries. The malpighian corpuscles were remarkably free from hemosiderin, but in a few of the pigment-laden spleens, a small amount of blue granular material was present in the reticular cells in the collar of lymphocytes. Occasionally, in the region of the connective tissue around the arteries and in the capsule and framework of the spleen, there was some diffuse blue or granular blue material. By far the greater portion of the hemosiderin was found in the large phagocytic cells of the pulp. A small amount was sometimes present within the endothelial cells lining the smaller veins. Where there had been excessive destruction of hemoglobin, the lumina of the veins usually contained considerable extracellular material. Usually, in the more moderate anemias, the pigment was largely intracellular and granular. The more rapid the catabolism of the hemoglobin, the more did the pigment containing iron tend to be diffuse instead of granular in this organ. In one case of a patient who had died after repeated transfusions of blood red cells of the blood could be seen in various stages of disintegration in the phagocytic cells.

<sup>33</sup> Mallory and Wright. Pathological Technique, ed. 8, Philadelphia, W. B. Saunders Company, 1924, p. 207.

*Liver* —In general, the spleen contained a greater amount of hemosiderin than did the liver. The blood in the portal veins contained varying amounts of hemosiderin, the amount and type being roughly proportional and similar to that found in the splenic veins. The greatest amount of hemosiderin was found periporally in varying amounts in both the Kupffer and the hepatic cells. Apparently, the more rapid the destruction of the hemoglobin, the more pigment containing iron was found in the Kupffer cells, whereas in the more chronic anemias the greater amount of hemosiderin was found in the hepatic cells. The nearer one approached the central vein the fewer were the blue granules in both the Kupffer and the hepatic cells. In two cases with excessive destruction of hemoglobin the capillary endothelium contained occasional blue granules, and free granules containing iron between the endothelium and the rows of hepatic cells. Also, in the hyperactive cases, the hemosiderin was occasionally found in the periphery of the hepatic cell, whereas in the more severe chronic anemias, it was usually lined up on the sides of the biliary canaliculi. In the cases of extremely hyperactive catabolism of pigment, granules of hemosiderin were definitely demonstrable in the lumina of the biliary ducts. Occasionally in large biliary ducts rows of fine granules of hemosiderin were seen in the protoplasm of the cells outside the nucleus, extending from the inner to the outer border of these lining cells. The central and sublobular veins sometimes contained from a small to a moderate amount of hemosiderin, most of which was extracellular and in fine granular form. Varying amounts of hemosiderin sometimes were to be found as granules or as diffuse material scattered in the region of the framework of connective tissue and in the adventitia of the arteries. In the younger persons, more deposit of pigment was noted in the Kupffer cells than in the elderly. Diffuse pigment containing iron was not found in the hepatic cell, but in the cases of hyperactive catabolism of hemoglobin, the Kupffer cells contained much of this variety of the pigment. The Kupffer cells contained insignificant numbers of ingested red cells of the blood or particles of hemoglobin as compared with the reticulo-endothelial cells of the spleen, lymph nodes and bone marrow.

Around the central vein, the bilirubin was found chiefly in the hepatic cells, while only occasionally in this region was there a moderate amount of the pigment in the Kupffer cells. When there was central necrosis and biliary stasis, the Kupffer cells around the central veins were sometimes gorged with bilirubin. The bilirubin sometimes occurred in considerable quantities in the hepatic cells with little or no hemosiderin present in the section, or there might be a considerable amount in evidence. In the latter case, there occurred an overlapping of the pigments, particularly in the midzonal area, and the pigments were sometimes found together in the same cell. The amounts of both

pigments were so considerable that they might be found together in all zones. Bilirubin in the hepatic cells was usually not associated with a demonstrable dilatation of the biliary canaliculi, although where plugs of bile were demonstrable in these canaliculi, considerable biliary pigment with plugs of pigment were found in the hepatic cells without hemosiderin. The cases of biliary stasis were associated with the largest amounts of bilirubin found in the Kupffer cells, although the Kupffer cells around the central vein might contain biliary pigment without evidence of the dilatation of a biliary duct or canaliculus. The biliary pigment was usually in the form of larger and smaller yellow brown, irregularly shaped granules and crystals, which were scattered throughout the cell except in the nucleus. Bilirubin was, of course, demonstrable in the biliary ducts, although the ducts were usually empty. Bilirubin was not demonstrable in the blood stream by this method.

*Lungs*—Pigment was usually not found in the pulmonary vessels but there might be a small amount, roughly proportional to the amount found in the sublobular veins in the liver. Most of this pigment was extracellular. More pigment was found in the smaller vessels. A definite but small amount was occasionally found in the cells lining the alveoli. Some of these cells were obviously in the process of being detached from the wall of the alveoli. Most of the pigment found in the lungs was in the intra-alveolar phagocytic cells and was present in amounts comparable with the number of red cells of the blood in the alveolar spaces. These phagocytic cells appeared, in most cases, to be other than those cells derived from the lining of the alveoli. A small amount of bilirubin was identified in occasional phagocytic cells in the alveolar spaces.

*Kidneys*—The persons dying of pernicious anemia were the only ones having pigment in the kidney. Of the nine cases studied, five showed more or less hemosiderin in the kidney and four were free from pigment containing iron. The iron was present chiefly in the cells lining the proximal tubules, although, in some cases, the diffuse pigment present in the lumina of the proximal tubules and in the glomerular spaces was greater than that found in the cells. Some bilirubin was demonstrable in the cells of the proximal tubules.

*Bone Marrow*—Hemosiderin in the diffuse and the granular form was usually present. It was chiefly within the large reticulo-endothelial cells, which, in the pigment laden cases, appeared to be somewhat regularly spaced. A small amount of hemosiderin was found also in the endothelial cells lining the smaller sinuses. A small amount of bilirubin was identified.

*Spleen*—Neither hemosiderin nor bilirubin was identified.

*Pancreas*—Pigment that could be identified was not seen.



TABLE 1—*Estimated Amounts of Hemosiderin (Hs) and Bilirubin (Bt) Found in the Hepatic Cells and the Kupfer Cells of the Liver and in the Tissues of the Spleen, Kidney, and Other Organs of 71 Persons Coming to Autopsy Following Death from Various Causes*

Sex	Age	Hours Post mortem	Cause of Death	Hepatic Cells		Kupfer Cells		Spleen		Kidney		Other Organs (Markedly fatty liver)
				Hs	Bt	Hs	Br	Hs	Bt	Hs	Br	
M	39	1	Acute hemolytic pancreatitis delirium tremens	00+	00+	+	00+	000+	0			
M	56	3	Toxic adenoma	0+	++	+	00+	++	0			
F	34	1½	Bronchiectasis, postoperative thoracoplasty	0	+	0	000+	0	0			
M	1	26	Tracheotomy for papilloma of larynx, pneumonia	0	+	0	00+	000+	0			
F	4	10	Traumatic hemorrhage into brain	00+	0	000+	0	000+	0			
M	70?	12	Carcinoma of bladder, perinephritic abscess	++	++	++	00	++	0			
M	25	3	Postoperative appendicitis, general peritonitis	000+	++	000+	00	0	0			
F	60	?	Arteriosclerosis, cardiac hypertrophy and dilatation	00+	+	0	00+	00+	000+			
F	50	36	Malignant ulcerative endocarditis	0	++	0	0	000+	0			
M	60	6	Hypernephroma	0	++	000+	0	++	0			
M	70	7	Skull fracture	000+	++	++	000+	00+	0			
M	50	12	Amphotrophic lateral sclerosis, pneumonia	+++	+	++	0	++	0			
F	15	1	Disseminated tuberculosis of lungs, peritoneum and meninges	00+	00+	000+	0	++	0			
F	2	6	Nephritis	0	+	0	0	++	0			
M	60	3	Carcinoma of stomach	0	++	0	0	000+	0			
M	10	7	Postoperative brain hemorrhage, adipose genital dystrophy	0	0+	0	00+	0	0			
F	25	10	Chronic peritonitis, abscess of brain	++	0+	0+	0	++	0			
M	67	12	Arteritis, cardiac hypertrophy and dilatation	+	+	+	0	+	0			
M	65	½	Abscess of lungs	+	+	00+	0	+	0			
M	65	3	Arteritis, cardiac hypertrophy and dilatation	0	+	0	0	++	0			
M	55	2	Arteritis, cardiac hypertrophy and dilatation	0+	+	0+	0	00+	0			
M	66	1	Carcinoma of prostate, pneumonia	++	+	0+	0	00+	0			
F	1	12	Acute pericarditis, pneumonia	000+	000+	000+	0	00+	0			
M	47	5	Perforating gastric ulcer, pneumonia	0+	++	00+	000+	++	000+			
F	68	8	Carcinoma of ovary, jaundice	0+	++	++	0+	++	000+			
F	60	2	Sarcoma of ovary, pneumonia	+	+	+	000+	++	0			
M	57	9	Toxic adenoma, pneumonia	+	+	+	00+	++	0			
F	16	15	Congenital syphilis, osteomyelitis, peritonitis pneumonia	+	+	+	00+	++	0			
M	40	16	Peritheloma of pituitary gland, pneumonia	0	+	0+	0	+	0			
M	65	9	Carcinoma of pancreas, jaundice	+	+	+	0	++	000+			
F	48	17	Chronic nephritis, cardiac hypertrophy and dilatation	0	+	0+	0	++	0			
M	28	1	Diverticulitis, peritonitis, pneumonia	+	0+	000+	0	++	0			
M	10	2	Cardiac hypertrophy and dilatation, abscess of lung	0	00+	0	0+	0+	0			
F	64	2	Cerebral hemorrhage, pneumonia	0	+	0	0+	0+	0			
M	73	4	Lobar pneumonia	0	000+	0+	000+	++	0			
M	47	1	Acute vegetative endocarditis pneumonia	++	++	+	0	++	0			
M	27	24	Chronic ulcerative colitis, peritonitis	0	+	0	0	00+	0			

Suprarenal gland, 0

T	24	1	A	Tubercular empyema, postoperative thoracoplasty	0	+	0+	0	++	0		
M	10	10	A	Vegetative endocarditis, cardiac hypertrophy and dilatation	0	+	00+	0+	0+	0		
I	53	12	A	Toxic adenoma, pneumonia	0	+	00+	0+	0+	0		
I	16	14	A	Empyema, postoperative thoracoplasty	000+	+	+	00+	+	000+		
T	68	18	A	Cerebral hemorrhage, pneumonia	000+	00+	0	0	00+	0		
M	13	12	A	Leukosarcoma, intestinal obstruction	000+	0+	000+	0	000+	0		
M	76	34	A	Portal cirrhosis, chronic myocarditis	000+	000+	++	++	++	000+		
M	56	1	A	Cardiac hypertrophy and dilatation, pneumonia	+	+	+	+	++	000+		
T	15	12	A	Diabetes mellitus, tendon sheath infection	+	+	+	+	+	0		
M	5	14	A	Meningitis	+	+	+	+	+	0		
M	70	34	A	Carcinoma of jaw, abscess of lungs	0+	0+	+	0	+	0		
M	75	14	A	Cardiac hypertrophy and dilatation, pneumonia	000+	+	0	00+	+	0		
T	21	1	A	Pneumonia	0	+	0	00+	+	0		
T	21	24	A	Miliary tuberculosis	0+	+	+	0	+	0		
M	15	14	A	Postoperative carcinoma of colon, general peritonitis	0	+	0	00+	+	0		
M	62	?	Z	Carcinoma of jaw, pneumonia	++	+	+	0	++	0		
M	50	8	Z	Carcinoma of stomach, pneumonia	0	+	+	000+	0	0		
M	56	11	Z	Syphilitic aneurysm, hemorrhage in lung	0+	00+	0+	00+	+	000+		
M	15	24	A and Z	Alcoholic leukemia, repeated transfusions	++	0+	++	0+	++	00+		
M	15	24	A	Alcoholic leukemia, intestinal obstruction	0	+	0	000+	+	0		
?	?	?	Z	Periculous anemia						0		
?	?	?	Z	Periculous anemia						+		
?	?	?	Z	Periculous anemia						+		
T	?	2	Z	Periculous anemia				+	0	+		
M	70	14	Z	Periculous anemia, cardiac hypertrophy and dilatation						+		
M	29	?	Z	Periculous anemia, fibrous myocarditis						0		
M	58	1	Z	Periculous anemia, cardiac hypertrophy and dilatation	++	++	+	000+		0		
T	67	3	Z	Periculous anemia, rheumatic endocarditis, pneumonia	+	0+	++	000+		0		
M	65	2	A	Periculous anemia, on Mot diet one year, pneumonia	+	+	+	0	+	0		
?	?	?	Z	Leukemia	++	++	+	+	++	+		
M	3 days	?	Z	Patent interventricular septum, imperforate anus	+	0+	++	0	++	0		
M	27	1	Z	Stricture of bile ducts, jaundice	+	++	0+	00+	++	0		
M	15	?	Z	Postoperative fibroma of brain	++	+	+	0	+	0		

Kidney, lungs, 0000, suprarenal glands, p. increases, 0000, bone marrow, Hs 000, Br 0  
Lung, 0, suprarenal gland, 0  
Bone marrow, Hs +++, Br 000+, lymph node, Hs +++, Br 00+, pancreas, 0, heart, 0  
Bone marrow, Hs 00+, Br 0, lung, 0

Suprarenal gland, 0, pancreas 0  
Lung, Hs 0+, Br 0, suprarenal gland, 0  
Lung, 0  
Pancreas, 0, suprarenal gland, 0  
Lung (phag), Hs +++, Br 0

\* A = alcohol, Z = Zenker formaldehyde solution

*Lymph Nodes*—In the one case of a person dying after frequent transfusions, the sinuses of the leukemic lymph nodes contained many phagocytes filled with red cells of the blood and diffuse and granular hemosiderin. In these cells, an occasional granule was seen simulating bilirubin.

Little additional information was obtained from the study of rabbit tissues. Hemoglobinuria occurred in every instance in which hemolyzed serum had been injected. It was always marked enough to turn the urine a reddish black. The benzidine test was always markedly positive in these cases. In two cases urines collected from eighteen to twenty-four hours after the last injection were negative grossly and to benzidine after previous samples obtained from the same sources had been positive. In the first rabbit, a small amount of hemosiderin was found within the tubules, one cast being loaded with many granules of hemosiderin. Except for this evidence of hemosiderinuria, the animals used as controls contained quite as much pigment as did the rabbits into which hemolyzed serum had been injected. In the case of the rabbit which died following the injections of hemolytic serum, the cause of death was a complicating enteritis following a slight anemia. The day before the rabbit's death the blood count showed 5,120,000 red cells and the hemoglobin content was 80 per cent. The urine of the bladder was normal according to the benzidine test.

#### INTERPRETATION

The histochemical evidence pointed to the probability that the reticulo-endothelial cells, particularly those of the spleen and the bone marrow, with the Kupffer cells and the large wandering phagocytes being the chief cell reserve, break down the hemoglobin into bilirubin, and transfer it to the hepatic cells, where it is excreted into the biliary canaliculi. It could not be said with certainty that catabolism of pigment does not take place to some small degree in the hepatic cells.

#### COMMENT

Because the methods of histochemical study were not able, in some cases, to show the presence of pigment, I think that the breaking down of hemoglobin into bilirubin normally occurs in solution within the cells. I assume that wherever the pigments, hemosiderin or bilirubin were found, it was evidence of an excessive destruction of hemoglobin or of an interference with the excretion of it from the hepatic cells. I also assume that this visible pigment was in the same location in which the transformation normally takes place in solution or that it was in the process of transportation, the only difference being that this visible pigment was increased sufficiently above the normal to become evident in the process of fixing and staining. Most of the interpretation is based

TABLE 2—*Estimated Amounts of Hemosiderin (Hs) and Bilirubin (Bt) Found in the Various Tissues of 1 Dog That Died After Overtransfusion, and of 10 Rabbits Into Which Varying Doses of Serum from Hemolyzed Blood of Rabbits Had Been Injected at Various Intervals of Time The Solution of Hemoglobin Used Was Approximately One Fourth of the Strength of the Serum Made Isotonic After Laking the Blood in Distilled Water*

Rabbit	Sex	Weight	Injection of Solution of Hemoglobin	Lapse of Time Between Last Injection and Autopsy	Hepatic Cells		Kupffer Cells		Spleen		Kidney		Bone Marrow		Lung		Heart and Suprarenal Gland	
					Hs	Br	Hs	Br	Hs	Bt	Hs	Br	Hs	Br	Hs	Br	Hs	Br
1	F	2,640	5 cc 9 a m, 5 cc 11 a m, 5 cc 1 a m, 10 cc 3 a m	30 min	000+	00+	000+	0	+	0	000+	0	0+	0	000+	0	0	0
2	F	3,250	20 cc	12 hrs	0	0	0	0	+	000+	0	0	000+	0	0	0	0	0
3	M	3,520	20 cc	24 hrs	00+	0+	0	0	+	0	0	0	0+	0	0	0	0	0
4	F	4,120	20 cc	1 hr	000+	0+	0	0	0+	0	0	0	000+	0	0	0	0	0
5	F	3,120	(Bled to death, blood made up into solution of hemoglobin, used as control)		0	0+	0	0	+	0	0	0	0	0	000+	0	0	0
6	F	2,960	6 cc every 15 minutes for 10 injections	15 min	0	+	0	000+	+	000+	0	0	0+	00+	0	0	0	0
7	F	2,000	6 cc every 15 minutes for 12 injections	15 min	0	+	0	000+	+	0	0	0	00+	000+	0	0	0	0
8	F	2,710	6 cc every 15 minutes for 12 injections	15 min	0	0+	0	0	0+	0	0	0	000+	0	0	0	0	0
9	F	2,350	(Bled three times, died)		0	0	0	0	+	0	0	0	000+	0	0	0	0	0
10	M	3,650	(Antihemolytic serum injected, died)		000+	0+	0	0	0+	000+	0	0	00+	000+	0	0	0	0
Dog 1	M		(Died after overtransfusion, tissues fixed in alcohol)		00+	000+	000+	0	+	000+								

on the location and the type of the pigment containing mon, as the bilirubin was less satisfactorily identified

As indicated by the presence of the pigments, the only cells involved in this catabolism of hemoglobin were the hepatic cells, the Kupffer cells, the reticulo-endothelial cells of the spleen and the bone marrow, and to a less extent, the endothelial cells of the larger sinuses of the bone marrow and the smaller veins of the spleen, the fixed phagocytes and the cells of connective tissue of the stroma of the liver and the spleen and of the adventitia of the arteries in these organs, the phagocytes of the lung alveoli, and the alveolar epithelium

Particularly in the cases associated with the phenomena of agglutination, I saw the red blood cells ingested chiefly by the reticulo-endothelial cells of the spleen and the bone marrow and by the large wandering phagocytes, considered to be a part of the reticulo-endothelial system, that were picked up in the lymph nodes. I saw hemoglobin or parahemoglobin<sup>34</sup> and hemosiderin side by side in these cells, and because of the work of Rich,<sup>32</sup> who visualized the process in the cells of cultures of tissues, and Lowit<sup>31</sup> and others, I felt confident that these pigments were undergoing transformation within these cells. I felt, therefore, that normally the reticulo-endothelial cells of the spleen and the bone marrow were the most active in manufacturing biliary pigment from hemoglobin, and that in the emergencies the large wandering phagocytes became active in the catabolism of pigment. In one case with an infarct of the spleen, bilirubin was present in considerable quantities, the transformation having been completed in these cells without the usual facilities being present for the rapid removal of the bilirubin. From these reticulo-endothelial cells, the biliary pigment was probably liberated into the plasma and hurried through the Kupffer cells or the endothelial cells into the hepatic cells and excreted into the biliary canaliculi. When hemosiderin was produced in excess extra-hepatically, it was liberated in the plasma or carried by the reticulo-endothelial cells to the liver, where the Kupffer cells took up the pigment and possibly transformed some of it to bilirubin, but at least, in many instances, they passed much of it on to the hepatic cells unchanged. It was not proved that the Kupffer cells picked up any bilirubin from the plasma. It might be that the endothelial cells were the avenue of approach for the bilirubin on its way to the hepatic cells.

Recent work of Jaffé and Berman<sup>35</sup> led me to believe that for the foreign pigments excreted through the hepatic cells, the Kupffer cells

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34 Brown, W. H. Observations on the Origin, Distribution and Significance of Fuchsin Bodies, with Special Staining Technique, *J. Exper. Med.* **12** 533, 1910

35 Jaffé, R. H., and Berman, S. L. Functional Studies on the Relation Between Kupffer Cells and Liver Cells. Address delivered before the Chicago Institute of Medicine, 1928

and the hepatic cells act as a unit, the stellate cells of Kupffer picking the pigment out of the blood stream and passing it on to the hepatic cells. Jaffe demonstrated this with his injections of oleokoniol, a very finely emulsified fat. In this experiment, the fine particles of fat were seen to be picked up by the stellate cells and at a later stage, passed on to the hepatic cells, then disappearing. I take it that the hemosiderin was the foreign type of pigment, requiring the assistance of the Kupffer cells. The work of Tarchanoff<sup>28</sup> and others would indicate that the hepatic cells require no assistance with bilirubin. With slight obstruction of the biliary ducts, one would expect to find the bilirubin appearing first around the central vein and if it is in excess one would expect that it would involve cells nearer the portal vein and would then overflow into the Kupffer cells and later into the plasma with resultant jaundice of other tissues. My observations concurred with such a picture and not with the picture that would indicate that bile is picked up by the stellate cells from the plasma after being liberated by reticulo-endothelial cells elsewhere.

The large wandering phagocytic cells are probably the reserve of the reticulo-endothelial system. The more excessive the destruction of hemoglobin, the more prominent are these cells in the picture of the pigmentary catabolism. This might account for the difficulty that Lepelne<sup>17</sup> had in trying to get a complete and somewhat permanent block of the reticulo-endothelial system with injections of collaigol. The phagocytes of the more fixed tissues are probably accessory in picking up some of the granular pigment containing iron. On account of their proximity to the fibers of the connective tissue, it is probable that the excess of iron diffuses slightly into the protoplasm of the connective tissue and causes the light diffuse blue staining that they commonly show in the markedly hemolytic chronic cases.

Just what the pertinent function of the endothelial cells is, as opposed to the reticulo-endothelial cells mentioned which line the sinuses of the liver, spleen and bone marrow, and the epithelial<sup>36</sup> cells lining the alveoli is a matter of conjecture. At least, their importance is slight.

Because of obvious technical difficulties, it was not demonstrated that the hepatic cell without the Kupffer cell can ingest hemosiderin. In all the reticulo-endothelial cells, the evidence was that the ingested hemoglobin, the ingestion of which normally takes place in solution or as a result of fragmentation (Rous<sup>37</sup>) or less commonly following phagocytosis of red cells of the blood, breaks down into bilirubin within

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36 Fried, B. M. The Origin of Histiocytes (Macrophages) in the Lungs. An Experimental Study by the Use of Intratracheal Injections of Vital Stain, *Arch. Path.* **3** 751 (May) 1927.

37 Rous, Peyton, and Robertson, O. H. The Normal Fate of Erythrocytes, *J. Exper. Med.* **25** 651, 1917.

the cell and that the bilirubin is later eliminated into the plasma. In the hepatic cell, evidence was not present to indicate that hemoglobin is ingested at all, unless one assumes that the pigment containing iron represents the product of a breaking down of hemoglobin within that cell. That this is unlikely was indicated by the fact that hemosiderin in the hepatic cell was associated with hemosiderin in greater quantities in the spleen and the bone marrow. And usually there was an amount of hemosiderin in the Kupffer cells to indicate the passage of the pigment there. Furthermore, the pigment in the hepatic cells was always found to be strictly granular or irregularly crystalline, even in the cases of hyperactive hemolysis, and not diffuse. In all other locations where excessive catabolism of hemoglobin was taking place, the pigment became more diffuse than granular or crystalline. The granular-crystalline type indicated at least temporary storage in the cell.

As some of the granular hemosiderin was found in the biliary ducts, I inferred that a threshold level exists for hemosiderin in the hepatic cell. And as there were fine granules of hemosiderin in the cells of the larger ducts, extending from one end of the cell to another, and as these areas were separated from the hepatic cells by the connective tissue of the portal canal and blood vessels, I inferred that some resorption of the hemosiderin was taking place.

The fact that the two pigments were found side by side in the hepatic cell was shown to be at least largely a matter of overlapping of stored pigment, depending on a concomitant increase in hemolysis and an interference with the excretion of biliary pigment. A case of pernicious anemia in which the patient had been treated satisfactorily over a period of a year by means of a diet high in liver, still showed a considerable deposit of hemosiderin and biliary pigment in the hepatic cells, although the bone marrow had lost its picture of pernicious anemia. This might indicate that the content of iron in the liver had been changed so that it was not easily dissociable. I did not obtain any histochemical evidence that this stored pigment is broken down into bilirubin, or that it is transformed into hemoglobin, or that as a residue of iron, or a changed pigment containing iron it remains stored in the hepatic cell.

In the case of the rabbits, I saw that the threshold of the kidney was such that large amounts of hemoglobin could be passed into the urine with little transformation into hemosiderin or bilirubin taking place in the body. That the threshold of the kidney was higher than the threshold of the hepatic cell for hemosiderin and bilirubin was indicated by the fact that hemosiderin and bilirubin were excreted into the bile before it was lost in the urine. The amount of hemosiderin found in the kidney indicated, in a given case,<sup>38</sup> the degree of hemosiderinuria.

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38 Rous, Peyton. Urinary Siderosis, *J Exper Med* 28 645, 1918.

The morphologic study of the site of the formation of the biliary pigment would be made more definite if adequate methods of staining were at hand for differentiating bilirubin from melanin and hemofuscin and miscellaneous brownish granules and crystal-like substances appearing in the several tissues. Lowit,<sup>31</sup> in his use of the frog, was able to differentiate fairly well between hemosiderin and bilirubin and biliverdin, because, in the cases of the latter two, pigments and crystals were easily and characteristically formed in this animal. There was some question whether or not, in the use of some of the old stock Zenker material, a loss or change had occurred in the ferrous or in the biliary pigment. In most cases, at least, I felt that only inconsequential changes had resulted.

Brown<sup>39</sup> found that hemosiderin could be formed during autolysis of the liver. In my series of cases the number of hours elapsing between death and the autopsy (from one-half to forty-four hours) did not have any apparent effect on the formation of this pigment.

#### SUMMARY

A study of the literature and the material from seventy-one autopsies, with use of the ferrocyanide reaction to differentiate catabolic products of hemoglobin giving the reaction of iron from bilirubin, which does not contain iron, was undertaken in an attempt to throw additional light on the site of the formation of the biliary pigment. Hemolyzed serum was injected intravenously into seven of ten rabbits, and the tissues were studied as in the case of the human material. The liver and the spleen of an overtransfused dog were likewise examined.

It was found that the cells of the "reticulo-endothelial system" and the hepatic cells were chiefly involved in the breaking down of hemoglobin, which normally take place in solution. It was observed that the reticulo-endothelial cells of the spleen and the bone marrow were the most active in breaking down the hemoglobin, and that the Kupffer cells of the liver and the large wandering phagocytic cells were perhaps the more important reserve of the "reticulo-endothelial system." It was found that the hepatic cells have a definite threshold for hemosiderin as well as for bilirubin, and that for both of these substances the threshold is lower than that of the kidney. The occurrence of the bilirubin and the hemosiderin in the same hepatic cell was found to be an overlapping dependent on a concomitant hyperactivity of hemoglobin catabolism with the consequent storage of hemosiderin in the liver, and on an interference with the excretion of the biliary pigment from the hepatic cells. The Kupffer cells were seen to "feed" the hepatic cells with hemosiderin, but contained only bilirubin as the result of a possible

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39 Brown, W. H. Changes in the Hemosiderin Content of the Rabbit's Liver During Autolysis, *J. Exper. Med.* **12** 623, 1910.



transformation from hemosiderin within the cell or of an overflow of biliary pigment from the hepatic cell. The indications were that the Kupffer cell-hepatic cell combination is of little importance in the formation of biliary pigment under normal rates of pigmentary catabolism. In general, it was found that the granular crystalline type of hemosiderin indicated ferrous material that was being at least temporarily stored while the more diffuse material giving a reaction of iron was in the process of active catabolism. The granular crystalline hemosiderin was always found in the hepatic cell. Both types were found in the reticulo-endothelial cells.

Evidence was not disclosed that the hepatic cell takes part in the manufacture of biliary pigment, but the possibility of a breaking down of hemoglobin within the hepatic cell has not yet been excluded.

# MIGRATION OF LEUKOCYTES IN BLOOD CLOTS

## I THE INFLUENCE OF PHOSPHATES OF SODIUM AND POTASSIUM<sup>1</sup>

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The properties of leukocytes which lead to one condition their migration include the physical character of their protoplasm, their chemical constitution, their adhesiveness, probably their electrical charge and perhaps certain other factors. It is probable that essentially the same factors, with minor modifications, influence phagocytosis by leukocytes, and that what applies to the one phenomenon applies almost equally to the other. The parts played by chemotaxis and alterations of surface tension are well known, but other influences of importance must also be involved. The differences of cellular reaction in varying manifestations of inflammation are probably of significance in the understanding of these manifestations and may perhaps aid in their control and relief.

Surface tension phenomena have long been called on to explain the mobility and the phagocytic properties of leukocytes, and, for the most part, correctly. That this gives the full explanation is open to doubt. Sawtchenko<sup>1</sup> stated that the approach of the cell to the object to be phagocytosed is a coagglutination, even though the act of englobement is due to alterations of surface tension. Tait<sup>2</sup> pointed out that such approach is observable in the case of nonmobile cells and inferred that the phenomenon is one of agglutination. Whereas bacterial agglutination shows the approach and adhesion of similar particles, the mutual approach of phagocyte and phagocytic object is that of dissimilar particles. That the mechanism of approach is electrical is suggested by various experiments, but it is difficult to determine the charge of the numerous particles that may thus approach. Abrahamson<sup>3</sup> assumed

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<sup>1</sup> Submitted for publication, Aug 14, 1928

<sup>2</sup> From the Hygienic Laboratory, U S Public Health Service, Washington, D C, and the Department of Pathology, Western Reserve University School of Medicine

<sup>3</sup> Sawtchenko, I G. Sur la theorie de la phagocytose, *Arch d sc biol* **15** 145, 1910

<sup>2</sup> Tait, J. Capillary Phenomena Observed in Blood Cells, Thigmocytes, Phagocytosis, Amoeboid Movement, Differential Adhesiveness of Corpuscles, Emigration of Leucocytes, *Quart J Exper Physiol* **12** 1, 1918-1920

<sup>3</sup> Abrahamson, H H. The Mechanism of the Inflammatory Process I The Electrophoresis of the Blood Cells of the Horse and Its Relations to Leucocyte Emigration, II Concerning the Adhesive Force of One Pseudopod of a Frog Leucocyte and Its Relation to Leucocyte Emigration, *J Exper Med* **46** 987 and 1003, 1927

that mammalian white cells are negatively charged and stated that they move with appreciable velocity under a potential difference of 1 volt per centimeter toward the anode. It would be difficult to state that all the objects phagocytosed are positively charged, which would seem to be necessary to the hypothesis that mutual approach is a simple electrical phenomenon. The introduction in this argument of diffusion or membrane potentials seems immaterial, in view of the fact that mutual approach may be observed under extremely simple conditions *in vitro*. It is not altogether certain that englobement is purely physical for Hamburger's<sup>4</sup> studies led him to believe that the effects are not due to surface tension but rather to alterations of the surface which influence the chemical processes within the cell body.

It has been known for years that leukocytes will migrate and adhere to solid surfaces such as glass, quartz, carbon and like substances, but will not do so in contact with greasy surfaces such as that of paraffin. The adherence and accompanying distortion, according to Tait, are a capillary phenomenon and their conditions have been extensively studied by Fenn<sup>5</sup>. Fenn showed that adhesiveness to glass is best at  $p_H$  7.8 to 8. Phagocytosis is best at  $p_H$  7. Phagocytosis of quartz increases with the acidity down to certain limits, whereas adhesiveness of leukocytes to glass increases with the alkalinity within certain limits. Also of interest is the fact that phagocytosis of quartz particles is favored by acid solutions and phagocytosis of carbon particles by alkaline solutions. However, the adhesiveness to coal is greater than that to glass in both acid and alkaline mediums. Measurements of the carbon electrode potentials and the cataphoretic charges on the particles failed to supply an adequate explanation for these various phenomena. As Loeb<sup>6</sup> pointed out, the consistency of the protoplasm plays a part in adhesiveness, since surface forces must be influenced by variations in the degree of solidity of the cell.

Looking to pure science for further information one hardly finds proof for the general assumption that cohesion, adhesion and molecular attraction in general are due to electrical phenomena. Thus, the diffi-

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4 Hamburger, H. J. *Physikalisch-chemische Untersuchungen ueber Phagocyten, Ihre Bedeutung von allgemein biologischen und pathologischen Gesichtspunkt*, Munich, J. F. Bergmann, 1912.

5 Fenn, W. O. The Phagocytosis of Solid Particles, *J. General Physiol.* **3** 439 and 575, 1921, *ibid.* **5** 311, 1923, The Adhesiveness of Leucocytes to Solid Surfaces, *ibid.* **5** 143, 1922, Effect of Hydrogen Ion Concentration on the Phagocytosis and Adhesiveness of Leucocytes, *ibid.* **5** 169, 1922, The Mechanism of Phagocytosis, in Jordan, E. O., and Falk, I. S. *The Newer Knowledge of Bacteriology and Immunology*, Chicago, University of Chicago Press, 1928, chap. 65.

6 Loeb, L. Amoeboid Movement, Tissue Formation and Consistency of Protoplasm, *Science* **53** 261, 1921.

culty in correlating the presumed negative charge of the leukocyte and the apparent negative charge of some of the particles phagocytosed on surfaces to which adhesion is manifest may be referred to the phenomena of molecular attraction, cohesion and adhesion, without reference to the electrical potential of the bodies concerned

The present study is concerned with the migration of human leukocytes through a homologous blood clot to a glass surface and their adherence thereto. The method devised by Wright<sup>7</sup> has been modified to provide more precise control of the conditions, particularly as comparative measurements have had to be made

#### METHOD OF STUDY

Wright placed agar slabs, from 1 to 2 mm thick, from which a circular cell 7 mm in diameter, had been cut away, on clean microscopic slides. Blood was placed in the cell, a cover-slip was applied over the cell and the preparation was incubated. The agar was then prized off and the clot was shaken off. The slide was washed in running water and the adhering leukocytes were fixed and stained. Wright did not mention the  $p_H$  of the agar. Wolf used an agar slab as the base as well as the wall of the cell, and in certain instances added  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  to bring the agar to the neutral point to litmus.

In the present series, new glass slides were soaked in 95 per cent ethyl alcohol for not less than twenty-four hours. They were then washed in distilled water and dried with a clean towel. Strip agar was cut into pieces from 1 to 2 cm in length, washed in running tap water for from eighteen to twenty-four hours, put through three changes of distilled water and melted in the proportion of 25 Gm of dry agar to 100 cc of distilled water. Freshly prepared agar was used in all the reported experiments. This usually titrated colorimetrically  $p_H$  6.7 to 6.9. In order to conserve blood, we cut the cells 4 mm in diameter. The slabs were  $1.5 \pm 0.05$  mm in thickness. The casting was done between two slides, separated at the ends by small pieces of slide, the thickness of which was measured by a Zeiss calibrator. The blood was taken by puncture from a finger into a paraffin chamber and mixed with a paraffined pipet, and after enough for all the cells was drawn up into the pipet, it was discharged in irregular order into the cells. This assured reasonable uniformity in the contents of all the cells. Less than one minute elapsed from the time of withdrawal to the time of filling all the cells. Technical difficulties made it unwise to use more than ten cells. The slides were warmed and kept warm on a coil of glass tube through which warm water was circulated. The temperature of the slides was from about 35 to 39 C. Incubation at 38 C was continued in a moist chamber for forty-five minutes. In order to assure ready removal of the agar, we first placed on the slide a strip of thin tinfoil with a circular perforation 8 mm in diameter. This allowed close approximation of the agar to the slide. After incubation, the strip of tinfoil, together with agar and cover slip and, in practically all instances, the clot also, was lifted from the slide. The slide was immersed in distilled water in a Coplin jar. After the red blood stopped diffusing, the material was fixed in saturated mercuric chloride solution, washed and stained.

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<sup>7</sup> Wright, A. E. The Study of Emigration and of the Bactericidal Effects Exerted in the Wound by Leucocytes, *Lancet* **1** 129, 1918. Wright, A. E., and Colebrook, L. Technique of the Teat and Capillary Glass Tube, Constable & Company, London, 1921.

with alkaline methylene blue (methylthionine chloride, U S P) Fixation with methyl alcohol and staining with Maximow's azure eosin were found to be equally satisfactory

Incubation for forty-five minutes at 38 C was found to be the optimal procedure Less time did not permit as great migration, and greater time rendered difficult the distinction between polymorphonuclear and mononuclear cells

In order to determine the influence of gravity on the migration of cells, we incubated certain series with the slides inverted The results indicate that gravity plays but a small part in the phenomenon, almost as many cells were found adherent to the slide in the inverted position as in the usual position This was to be expected, in view of the horizontal migration shown in the glass lath method of Wright

A series of experiments was conducted in order to determine the amounts of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  necessary to alter in certain degrees the  $p_{\text{H}}$  of agar<sup>8</sup> It was found that the ordinary soaking in water produces an agar, the  $p_{\text{H}}$  of which varies considerably Therefore, high grade agar strips were cut in pieces from about 1 to 2 cm in length, washed for from eighteen to twenty-four hours in running tap water, washed three times in distilled water and melted in distilled water in the Arnold sterilizer With triply distilled water the  $p_{\text{H}}$  varied between  $p_{\text{H}}$  6.7 and  $p_{\text{H}}$  6.9 It was found that standing at room temperature for a period of two weeks increased the acidity considerably Therefore, freshly made agar was always used With this as a primary mixture, the amounts of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  in 5 and 10 per cent solution were added drop by drop to the agar in the proportion of so many tenths of cubic centimeters of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  solution to 9 cc agar The volume was brought to 10 cc by the addition of distilled water It was found that a fairly satisfactory curve could be established, so that by the use of specified amounts of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  the  $p_{\text{H}}$  could be predicted with only slight error

The small quantities of blood employed made it difficult to determine how far the  $p_{\text{H}}$  of the blood is altered by the salt concentrations in the agar The following experiment does not give a precise indication as to what happens to the blood but shows clearly that diffusion occurs Agar cells were made in the usual way Each cell was filled with distilled water containing from two to three times the usual amount of indicator, and a cover slip was applied The same concentration of indicator was used in a series of tubes of different hydrogen ion concentrations A drop of each of these was placed on a large white porcelain plate, and color comparisons were made with the contents of the cells The indicators were bromthymol blue, phenol red and cresol red, indicated in the tables by the letters *BTB*, *PR* and *CR* The colors in the cells began to show at the margins immediately and were completely diffused throughout the cells at room temperature in from two to three minutes Tables 1 and 2 show readings of duplicate cells at two intervals of time

Each of the experiments was repeated at approximately the same room temperatures, with essentially the same results Two similar experiments with  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  were performed at incubator temperature for thirty and forty-five minutes, respectively, also with essentially the same results

Thus, diffusion from the agar into water occurs rapidly at room temperature, and within a few minutes the  $p_{\text{H}}$  of the water is, within the limitations of the method, the same as that of the surrounding agar The fact is not altered by an incubator temperature of 38 C

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<sup>8</sup> The phosphate salts used throughout the experiments reported in this paper were of high quality and were recrystallized twice or three times in the Chemical Laboratory of the Hygienic Laboratory

The number of leukocytes adhering to the slides with the different concentrations of a  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  in the agar could be compared fairly well with the naked eye, but the extent of distribution could not be determined except with the microscope, especially because with the weaker concentrations and with the more acid hydrogen ion concentration, the leukocytes are concentrated in the middle of the circle. It was therefore necessary to measure the circles and count the cells by use of the microscope. A Zeiss ocular micrometer was calibrated against an object micrometer. The extent of two diameters of the somewhat distorted circle was measured and the cells counted in the same diameters. The large square on the ocular micrometer corresponded to a square 0.2 mm on each side, with the tube at 15 cm, a 10 $\times$  ocular and a 4 mm objective. In the totaling of the number of

TABLE 1—*Experiment with  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  at 26 C*

Number	$p_{\text{H}}$ of Agar	$p_{\text{H}}$ of Water in Cells			
		First Reading *		Second Reading	
1	6.8	BTB 6.7	BTB 6.8	6.8	6.8
2	7.1	BTB 7.2	BTB 7.2	7.2	7.2
3	7.2	BTB 7.2	PR 7.2	7.2	7.3
4	7.6	PR 7.6	CR 7.5	7.6	7.5
5	8.0	CR 8.1	CR 8.0	8.1	8.0
6	8.3	CR 8.4	CR 8.4	8.4	8.4

\* With BTB (brom-thymol blue), the readings were at 5 and 39 minutes, with PR (phenol red), at 2 and 39 minutes, and CR (cresol red), at 1 and 28 minutes.

TABLE 2—*Experiment with  $\text{K}_2\text{HPO}_4$  at 25 C*

Number	$p_{\text{H}}$ of Agar	$p_{\text{H}}$ of Water in Cells			
		First Reading *		Second Reading	
1	7	BTB 6.9	PR 6.9	6.9	6.9
2	7.1	BTB 7.1	PR 7.1	7.1	7.1
3	7.1	BTB 7.2	PR 7.2	7.1+	7.1
4	7.5	PR 7.6	CR 7.5	7.6	7.5
5	8	CR 8.1	CR 8.1	8	8
6	8.3	CR 8.3	CR 8.3	8.3	8.3

\* With BTB (brom thymol blue), the readings were made at 3 and 25 minutes, with PR (phenol red), at 3 and 23 minutes, and CR (cresol red), at 3 and 19 minutes.

squares counted, one was eliminated, as it was duplicated in the crossing of the two diameters. The deduction amounts to one average square.

The protocol of a typical experiment is given in tables 3 and 4.

#### OBSERVATIONS

Table 4 is given in order to indicate the method in detail. Four experiments with  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  were performed, including that recorded in tables 3 and 4. The results of the four experiments are summarized in table 5.

With the exception of the figure for number 3 in experiment 2, the records in table 5 indicate that within the limits of the experiments, the greater degrees of alkalinity appear to favor greater migration of leukocytes. In experiment 4, the slides were incubated upside down. It is not thought that the method is so accurate that differences of from 1,000

to 2,000 are significant, but the extremes shown are well beyond the margin of error and the intervening figures fit the conclusion

It might be thought that the increasing number of cells with the decreasing acidity of the mixture is due to increased adhesiveness of the cells or to decreasing consistency of the clot. That the  $p_H$  of the blood clot is the same as that of the agar is not assumed, but that the blood clot

TABLE 3—Experiment with  $Na_2HPO_4 \cdot 2H_2O$ 

Number	$Na_2HPO_4 \cdot 2H_2O$	$Na_2HPO_4 \cdot 2H_2O$ Percentage	$p_H$ Expected	$p_H$ Found
1			6.7	6.8
2	5% solution	0.05	6.9	7
3	0.1 cc			
4	0.2 cc	0.1	7.2	7.1
5	10% solution	0.2	7.6	7.4
6	0.2 cc			
7	0.5 cc	0.5	7.8	7.8
8	1 cc	1	8.2	8.2

TABLE 4—Counts of Leukocytes

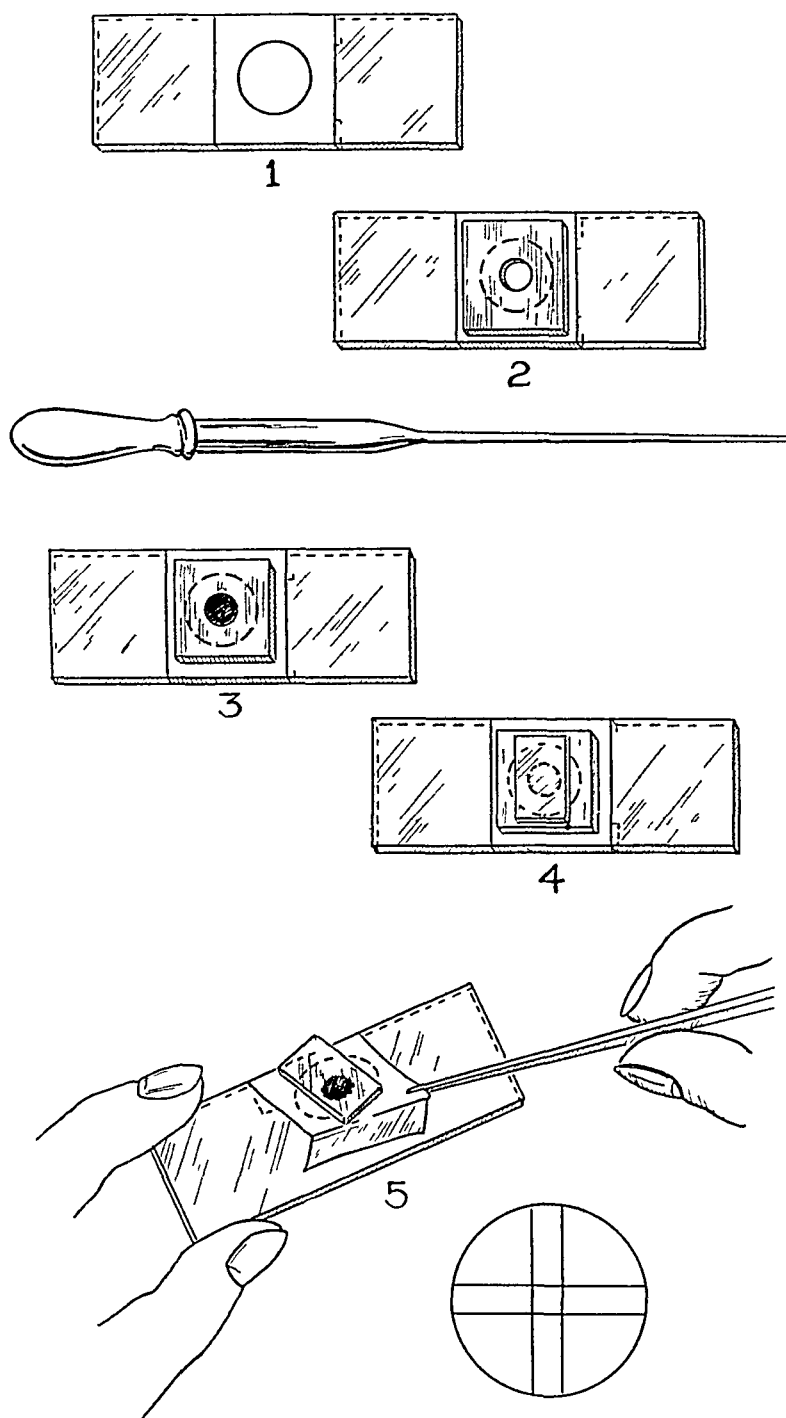
No	Squares			Leukocytes			Per Square Millimeter	Per Circle
	Vertical	Transverse	Total	Vertical	Transverse	Total		
1	Scratched							
2	20.5	16.5	36	893	804	1,643	1,139	12,244
3	20.3	17.6	36.9	1,112	933	2,045	1,385	15,512
4	19.9	19.6	38.5	943	1,061	2,007	1,200	15,725
5	20	16.8	35.8	1,377	1,152	2,529	1,766	18,780
6	19	18.8	36.8	1,528	1,418	2,946	1,996	22,400

TABLE 5—Summary of Four Experiments Showing Influence of  $Na_2HPO_4 \cdot 2H_2O$  on Migration of Leukocytes in Homologous Blood Clot

Number	Experiments							
	1		2		3		4	
	$p_H$	Leukocytes	$p_H$	Leukocytes	$p_H$	Leukocytes	$p_H$	Leukocytes
1			6.7	11,820			6.8	15,254
2	7	12,244	6.8	14,220	7	10,213		
3	7.1	15,512	7.4	19,400	7.1	11,033	7	20,115
4	7.4	15,725	7.5	16,760	7.4	11,573		
5	7.8	18,780	7.6	15,630	7.8	14,835	7.9	23,097
6	8.2	22,400			8.2	19,842	8.1	22,940

by diffusion of the phosphate becomes relatively more alkaline cannot be doubted, especially in view of the rapid diffusion into water. Yet Fenn found that in the presence of serum, the adhesiveness decreases with higher degrees of alkalinity. Figures have not been obtained as to the consistency of clots at different hydrogen ion concentrations, and the determination has not been made because of the further work with potassium phosphate.

In order to ascertain whether the cation or anion was the significant factor, a series of experiments was made using  $K_2HPO_4$  instead of



The slide with tin foil applied is shown in 1, and the agar slab superimposed in 2. In 3, the type of paraffined pipet for introducing blood into the agar cell is shown, and the cell filled with blood. In 4 the cover slip has been applied by pushing from the side. In 5 may be seen the removal of tin foil, agar, blood and cover slip. This is usually done with the slide inverted. The circle shows, within the straight lines, the diameters in which the cells are counted.



$\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  The 10 per cent solution of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  corresponds to 1.12 molar strength of sodium and 0.56 strength of phosphate. The solution of  $\text{K}_2\text{HPO}_4$  was made so as to give 1.12 molar strength of potassium and 0.56 molar strength of phosphate. Preliminary experiments showed that hydrogen ion concentrations of the agar mixtures can be predicted with the same relative degree of accuracy as with the sodium salts.

Table 6 gives the results of four similar experiments in which  $\text{K}_2\text{HPO}_4$  was used instead of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ .

In three of the four experiments, the maximum migration is at  $p_{\text{H}}$  7.5 and 7.6. In all, there is a more or less marked decrease in migration at  $p_{\text{H}}$  8.2. Thus the favorable influence of the more alkaline reaction observed with sodium salt is not apparent with the potassium salt.

The number of experiments is too small to permit the drawing of graphs, but the information obtained is confirmed by numerous experi-

TABLE 6—Summary of Results of Four Experiments Showing Influence of  $\text{K}_2\text{HPO}_4$  on Migration of Leukocytes in Blood Clot

Number	Experiments							
	1		2		3		4	
	$p_{\text{H}}$	Leukocytes	$p_{\text{H}}$	Leukocytes	$p_{\text{H}}$	Leukocytes	$p_{\text{H}}$	Leukocytes
1	6.8	18,845	7	21,801	7.2	18,089	6.8	21,250
2	6.9	14,377			7.2	18,910	7	21,850
3	7.1	19,406	7.1	28,602	7.3	20,040	7.2	16,600
4	7.5	25,119	7.5	23,206	7.6	20,476		
5	7.9	20,509	8	18,462	8	19,962	8	21,600
6	8.2	13,054	8.2	22,575	8.3	16,017	8.2	12,230

ments in which the gross examination confirms the general impression given previously.

It must be apparent that the migration and adherence of the leukocytes in the presence of serum is not dependent on the concentration of anion of the two salts, nor wholly on the hydrogen ion concentration. With the sodium salt, the optimal conditions, within the limits set up, are a concentration of 1 per cent and a  $p_{\text{H}}$  of 8 to 8.2. With the potassium salt, the optimal conditions are a concentration of about 0.2 per cent and a  $p_{\text{H}}$  of about 7.5.

Thus, attention must be directed toward the cations. Jacobs<sup>9</sup> stated that salts of the alkaline metals increase the permeability of cells to ions, the weak bases penetrate readily. It is well known that blood corpuscles generally contain little, if any, sodium and a goodly quantity of potassium, the reverse being true of plasma, but that the leukocytes share equally with the erythrocytes in this distribution is not established.

<sup>9</sup> Jacobs, M. H. Permeability of the Cell to Diffusing Substances, in Cowdry, E. V. General Cytology, Chicago, University of Chicago Press, 1924.

Hence, there are not any grounds for assumption in regard to differential permeability of these cells to the two cations concerned. Hamburger<sup>4</sup> found that sodium salts are more favorable to phagocytosis than are potassium salts, but did not offer convincing evidence of a reason for the difference. Whether the difference depends on influence within the cells or in the medium is not determined at present.

If the difference is due to alterations of adhesiveness of the leukocytes, this is not per se the result of the variations in hydrogen ion concentration. Observations of the slides made with the naked eye immediately after the clot was removed would indicate that the subsequent technical operations do not significantly alter the results.

In order to test the hypothesis that the salt concentration is of greater significance than the hydrogen ion concentration, it was determined to make a solution containing essentially the same concentration of sodium and phosphate as in the 10 per cent  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  buffer solution first employed, but so adjusted as to maintain the hydrogen ion concentration within a fairly narrow zone of  $p_{\text{H}}$ , not to exceed  $p_{\text{H}}$  7.1.

This was accomplished by making a mixture of solutions of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  and  $\text{NaH}_2\text{PO}_4$ . Thus, a 10 per cent solution of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  was made as before, which was calculated to be 1.12 molar in respect to sodium and 0.56 molar in respect to phosphate. A solution of  $\text{NaH}_2\text{PO}_4$  was made of the same molar strength as to sodium, but which, because of its composition, was necessarily 1.12 molar strength in respect to phosphate. To obtain this solution, 13.48 Gm of anhydrous  $\text{NaH}_2\text{PO}_4$  dried at 100 C and kept in a desiccator, was dissolved in 100 cc of distilled water. The final mixture was 83 cc of a 10 per cent  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  solution and 17 cc of  $\text{NaH}_2\text{PO}_4$  solution. This gave a buffer mixture of approximately  $p_{\text{H}}$  7 and is 1.12 molar strength in respect to sodium and 0.66 molar strength in respect to phosphate. The ratio of sodium to phosphate in the  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  solution is 1.12 to 0.56, and in the  $\text{NaH}_2\text{PO}_4$  solution is 1.12 to 1.12, but since the  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  predominates to a considerable extent over the  $\text{NaH}_2\text{PO}_4$  in the mixture, the ratio of sodium to phosphate is not greatly altered from that in the original 10 per cent  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  solution. It is 1.12 to 0.66 in the mixture, as compared with 1.12 to 0.56 in the original solution. The solution of the mixture of the two phosphates, therefore, is of the same molar concentration in respect to sodium as the original 10 per cent  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  solution, and the ratio of sodium to phosphate is not materially altered.

Preliminary experiments with the addition of this mixture to agar showed that varying concentrations produced a  $p_{\text{H}}$  in the agar which remained within the limits of  $p_{\text{H}}$  6.7 to 7.1. For the slight irregularities of  $p_{\text{H}}$  in the agar as shown in table 7, explanation is sought in the nature of agar as observed by Hoffman and Gortner,<sup>10</sup> who found that it contains small amounts of calcium combined with an agar acid, apparently an acid sulphuric ester and in our experiments a small precipitate was noticed in the agar, which was presumably calcium phosphate.

10 Hoffman, N. F., and Gortner, R. A. The Electrodialysis of Agar, *J. Biol. Chem.* 65: 371, 1925.

In setting up the experiments with blood, comparison was made between the effects of 0.1 per cent  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  and the effects of 0.1, 0.5 and 1 per cent mixtures of the two phosphates, as shown in table 7. The method was exactly the same in all details as in the earlier experiments, and the leukocyte counts were made in the same manner.

Table 7 shows that with 0.1 per cent  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  the  $p_{\text{H}}$  is slightly higher than with 0.1 per cent mixed salts, but in two of the three experiments the migration is about the same. A marked increase in the concentration of mixed salts, while not bringing the  $p_{\text{H}}$  quite up to that of the  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  again, resulted in a profound increase in the number of migrating cells. In two of the three experiments, this increased number is about the same for the 0.5 per cent and the 1 per cent buffer mixture in again. Thus, the conclusion is plain that under the circumstances of the experiment, the concentration of the salts is of more significance than the hydrogen ion concentration.

TABLE 7—Comparison of Effects of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  and Mixed Phosphates, Three Experiments

Number	$\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$	Experiments					
		1		2		3	
		$p_{\text{H}}$	Leukocytes	$p_{\text{H}}$	Leukocytes	$p_{\text{H}}$	Leukocytes
1	0.1% Mixture	7	4,444	7.3	7,370	7.3	5,597
2	0.1%	6.7	4,057	6.8	7,908	6.8	3,671
3	0.5%	6.9	15,283	7.1	8,672	7.1	14,303
4	1.0%	6.9	14,545	7.1	12,443	7.1	14,161

#### SUMMARY

The modification of the Wright method for studying the migration of leukocytes, here presented, gives a reasonably precise quantitative determination of migration. The important features are the use of tinfoil strips for removal of the agar, and washing in a Coplin jar instead of under running water.

When finally made into a gel, the  $p_{\text{H}}$  of agar is more constant after washing in running water than after soaking in still water. With a standard agar of this sort, the changes in  $p_{\text{H}}$  due to the addition of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  and  $\text{K}_2\text{HPO}_4$  can be predicted with a fair degree of accuracy.

Diffusion of phosphates from agar into water, and presumably into blood clot, in the agar cells occurs promptly.

The migration of leukocytes to the walls of the cells is a true migration influenced little by gravitation. Since the largest number of leukocytes adherent to the slide is different with different concentrations of the sodium and potassium phosphates, adhesion is probably not determined entirely by hydrogen ion concentration or salt concentration.

Migration in a positive sense is also indicated by reference to the number of leukocytes adherent to all the surfaces of the cells, as compared to the content of leukocytes in the blood. It is estimated that in those instances in which migration is most marked, about 55 per cent of the leukocytes are adherent, a phenomenon that is not to be harmonized with ordinary dispersion of leukocytes in the blood or on the surfaces of the clot.

When the  $p_H$  of the agar is altered by the addition of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ , the greatest migration of leukocytes occurs in the most alkaline  $p_H$  in a range between about  $p_H$  6.8 and  $p_H$  8.2. If  $\text{K}_2\text{HPO}_4$  is employed instead of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ , the greatest migration is in the medial  $p_H$ , namely about  $p_H$  7.5. Thus, the hydrogen ion concentration is not the sole or even the principal factor governing migration and adhesion. When  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  and  $\text{Na}_2\text{H}_2\text{PO}_4$  are mixed so as to maintain a fairly constant  $p_H$  with approximately the same ratio of sodium to phosphate, as in  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ , the addition of increasing quantities of the mixed salts leads to a marked increase in migration of leukocytes. Thus, the concentration of salt in the agar and presumably in the blood clot is of greater significance for migration of leukocytes than is the hydrogen ion concentration within the ranges studied.

# Laboratory Methods and Technical Notes

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## A PRACTICAL METHOD OF LABELING ANATOMIC SPECIMENS

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In tagging gross material for identification, it is desirable that the preparation of the tag should be a simple procedure, and that the number written or stamped on the tag should be resistant to handling in the presence of such substances as are commonly used in the preservation of gross material. Of the many different methods that have been designed, one especially in use is a method in which white celluloid is employed. As this method was used in the department of pathology of the University of Maryland, the numbers easily rubbed off in handling. Therefore, a scheme was devised of treating such labels with acetone thereby rendering the marking more permanent.

The celluloid used comes in sheets of various sizes, and may be obtained from almost any artists' supply house. It is white with one side unglazed for the purpose of marking. The tags are prepared by cutting the celluloid into pieces of the desired size and shape (a photograph trimmer may be used), and by punching a 3 mm hole near one end. The tags are marked on the unglazed surface with a lead or an indelible pencil or by means of an automatic stamping machine. Then, the tag is dipped into acetone for a brief moment. It may then be allowed to dry or it may be placed directly in water, from which it can be taken later for attachment to the specimen.

It has been found that, if the tags are treated with acetone, the numbers do not rub off in handling. In fact, it is difficult to scratch the numbers off. Acetone, being a rapid solvent of celluloid, brings about a covering of the carbon particles with a thin coat of celluloid. Tags made according to this method are satisfactory for specimens used in teaching, which are handled much by students, and for routine autopsy material, even though the organs after the washing, following kaiserling no 1, are placed in 95 per cent alcohol for two hours. Tags attached to specimens in kaiserling no 3 are still in perfect condition after six months. By experiment, it has been found that these tags will dissolve in absolute alcohol and 95 per cent alcohol. In this laboratory, enough water seems to be carried over from washing, after kaiserling no 1, to dilute the 95 per cent alcohol, so that the tags are not damaged in two hours. Tags placed in 80 per cent alcohol for several months have not shown any change in their numbers. In 10 per cent formaldehyde, they seem as permanent as though in water.

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\* Submitted for publication, Nov 7, 1928

\* From the Department of Pathology, University of Maryland School of Medicine

The method described is now regularly used in this laboratory for labeling routine necropsy material, specimens to be used in teaching, museum specimens and all surgical material. The tag is fastened to the specimen before it is placed in the museum jar. This has several obvious advantages over any label on the outside of the jar.

While this method may not be all that one could wish, yet it has the advantage of being simple and quick, and as permanent as the specimen. So far as I have been able to learn, this method has never been applied to labeling anatomic specimens, although a similar procedure may be employed in the manufacture of many celluloid articles, such as the small rule used so much in laboratories.

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### THE STABILITY OF GLYCERINATED ANTISHEEP HEMOLYSIN

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and BETTY SHIFMAN, Atlantic City, N. J.

While the method of Clock and Beard<sup>1</sup> for the preservation of antisheep hemolysin (that is, by the addition of 50 per cent by volume of chemically pure glycerol) is widely used, the literature records few observations of the duration of efficient preservation.

One of us,<sup>2</sup> in 1924, reported that glycerinated antisheep amboceptor that had been kept partly at room and summer temperatures, and partly in the icebox, was active and efficient after seven years.

This amboceptor has again been titered, twelve years after its original preparation (1916).

The original titer by Kolmer's method, using 0.3 cc of complement in the dilution of 1:30, was 1:20,000. After seven years, the titer was 1:16,000. The present titer, after preservation for twelve years, is 1:10,000 with 0.3 cc of complement in dilution of 1:30.

This observation, it is believed, will be of interest to those who desire to preserve antisheep amboceptor for long periods.

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Submitted for publication, Oct. 17, 1928.

<sup>1</sup> From the Laboratories of the Atlantic City Hospital.

1. Clock, R. O., and Beard, S. D. Preservation of Antisheep Hemolytic Amboceptor in Glycerol, *J. Infect. Dis.* **21**: 404, 1917.

2. Kilduffe, R. A. The Stability of Preserved (Glycerinated) Antisheep Hemolysin, *J. Lab. & Clin. Med.* **9**: 651, 1924.

# General Review

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## CELLULAR INCLUSIONS AND THE ETIOLOGY OF VIRUS DISEASES \*

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A filtrable virus manifests itself usually by the changes in structure or function which it causes certain cells to exhibit. The visible effect is often restricted, so far as is known, to only one type of cell, as in the lesions of molluscum contagiosum, in which only squamous epithelium of the skin is altered. The cellular changes which different virus diseases present may vary considerably and yet possess a certain similarity. Extreme effects may be illustrated by the rapid necrosis of ectodermal cells in a herpetic infection of the rabbit's cornea, and by the slow and prolonged proliferation of cutaneous epithelial cells brought about by the virus of the common wart. In between these extremes there are many gradations from progressive degeneration of cells, consistent for long periods with at least partial integrity and vitality, as in rabies, to an extremely rapid proliferation of cells which evokes a neoplasm simulating very closely a malignant tumor.

One virus, therefore, may operate so mildly on cells that its effect manifests itself only by a slightly increased rate of proliferation, where cellular reproduction normally takes place at a certain speed, and another may stimulate cells to a violent reproductive activity. In these cases there seems to be a change in the metabolism of the cells in such a way that it is not only consistent with vitality but greatly augments the vegetative function. Another virus may alter specifically the morphology of cells, increasing their size and shape, destroying more or less their differential characteristics, suppressing or altering their specific functions. Such changes are to be interpreted as evidences of disturbed cellular activities which are indicative of injury, and cells more severely injured may die and rapidly disintegrate. That the viruses inducing these phenomena act primarily on the cells has been demonstrated in many instances by the experimental studies of several investigators on a variety of material. Thus, following an inoculation of a rabbit's cornea with the virus of variola or vaccinia a hyperplasia of corneal epithelium and the appearance of Guarnieri bodies occur before there is any evidence of inflammation in the form of a cellular

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\* Submitted for publication, May 12, 1928

\* From the Department of Pathology of the Vanderbilt University School of Medicine

exudate (von Wasielowski, Rivers) In herpetic infection of the rabbit's cornea, Lipschutz has found typical intranuclear epithelial inclusions within seven hours, and before there is any other obvious reaction The lesion of herpetic encephalitis in the rabbit is characterized by the development of typical intranuclear inclusions within ganglion cells of the affected areas before there is any manifestation whatever of inflammation, and cellular exudate occurs only after these cells have begun to disintegrate (Goodpasture and Teague) Similarly, intracellular inclusions of rabies are the first evidence of an experimental infection of the rabbit's brain (Goodpasture) The lesion of molluscum contagiosum may proceed to maturity without a reaction in the corium, and the hyperplastic nodules of fowl-pox, developing in an animal without immunity, may show no inflammatory reaction until a resistance begins to develop, terminating eventually in complete immunity, if the animal survives the infection

It is very generally believed that viruses may alter primarily the activities and forms of cells It is further admitted that there may be a predilection on the part of a given virus for exerting its action on a certain type of cell This apparent specificity has led to the use of the term tropism in relation to virus infection Some viruses are thus said to be neurotropic, namely, herpes, rabies, poliomyelitis, others, epidermotropic, as variola-vaccinia, fowl-pox, molluscum (Lipschutz)

Again it has been demonstrated that a virus may increase, and it probably always increases, in quantity locally at the site of the specific changes it effects and in intimate relation with the cells which it alters Whether in a given instance the cells are incited to phenomenal growth or are rapidly destroyed, virus is multiplied within the lesion The major and probably the total increase seems to take place before the cell dies, and may diminish in proportion to the disappearance of the specifically altered cells (herpetic keratitis)

Two interpretations have been offered in explanation of the multiplication of viruses, according to the interpreter's conception of the nature of these agents, namely, that they are living things and reproduce themselves by vital activity, or that they are inanimate substances and are reproduced through an interaction between themselves and the cells which they alter (Sanfelice)

Since Iwanowski discovered that the active agent of tobacco mosaic will penetrate a filter which holds back certain bacteria, and Loeffler and Frosch found the same to be true of the virus of foot and mouth disease a great number of viruses have been shown to possess the property of filtrability through candles which are impermeable to ordinary bacteria And those who would hold that viruses are living things may conceive of them as exceedingly minute micro-organisms,



at least in certain stages of their development, or as possessed of qualities other than size which permit of their passage through the pores of filters

Many viruses which do not immediately kill the affected cell nor stimulate it to a rapid and continuous series of divisions, bring about peculiar structural changes within it. These changes are evidenced by the appearance of structures within the cytoplasm or within the nucleus, or both, more or less completely distinguishable from the normal cellular components, and distinctive enough to have been designated inclusions. The inclusions may be a prominent feature of those lesions induced by virus, which are constituted of a mixture of cellular proliferation and cellular degeneration, and which end spontaneously with the development of an immunity or terminate shortly in the death of the host.

It was only natural that the morphologist should have sought in the study of these intracellular bodies to find their relation to the etiologic agent at work, or to discover by means of them the peculiar activities which were taking place within cells under the influence of virus. Thus two opposed ideas have arisen, from morphologic evidence, regarding the nature of the cellular inclusions, namely, that they represent wholly or in part the virus itself, or that they consist of altered cellular constituents or products called forth by a reactive or destructive effect of the virus.

These two views are worthy of analysis with the accumulation of each additional bit of information, and especially so at the present time when there is relatively so little concentrated effort directed toward the study of virus diseases and perhaps a tendency to discount as valueless from an etiologic standpoint a considerable mass of morphologic evidence which has accumulated over a period of many years.

The inclusions of virus lesions have been studied probably most carefully, and by the largest number of investigators, in those animal diseases which are characterized by a pox or cutaneous eruption, namely, vaccinia, variola, sheep-pox, molluscum contagiosum and fowl-pox. Knowledge and theoretical considerations concerning the inclusions characteristic of the group of virus diseases have been obtained for each disease by similar processes, and a brief review of researches on the aforementioned infections will serve as a fair index of the type of investigation which has been pursued and the results obtained for the entire group of inclusions.

#### VARIOLA-VACCINIA

It is generally accepted that variola virus may be transformed into vaccine virus by a series of passages through the calf. The cytoplasmic inclusions incident to the two infections are similar in morphology and

are probably alike in composition. Recently it has been claimed by Gins that not only the virus of variola, but that of swine-pox, goat-pox and sheep-pox can be transformed into vaccine virus by several passages through the rabbit. This would indicate, in his opinion, that the aforementioned animal-poxes had their origin from variola. Van Heelsbergen has seemed to show that fowl-pox virus may similarly be transformed into that of vaccinia, and this view is supported by the experiments of Toyoda. The later work of Loewenthal, Kadowaki and Kondo, and of Andervont, however, seems to prove conclusively that at least the viruses of fowl-pox and of vaccinia have no such close relationship.

It is characteristic of the lesions of variola in man and in monkeys that inclusions occur within the nucleus as well as in the cytoplasm, while vaccinal lesions are characteristically associated with intracytoplasmic inclusions only. Since investigations of the two diseases have been largely parallel and the results practically identical, the two diseases are here considered together.

The inclusions of variola, although first carefully described and depicted by Guarneri in 1892, were undoubtedly seen by Weigert as early as 1874. Guarneri, employing the method of corneal inoculation of rabbits, first used in this connection by Straus, Chambon and Menard (1890), made a careful study of the inclusions of vaccinia. He concluded that they represent a protozoan parasite, which he named *Cytonhyctes vaccinae*. He thought he could discover ameboid motion in the inclusions when they were observed in corneal cells suspended in tear fluid. Two modes of multiplication were described, namely, by direct division and by formation of gymnosporos. The latter explanation of the mode was offered with reserve and later he discarded it, holding that these forms were degenerations.

The work of von Wasmann (1897 and 1901) confirmed the observations of Guarneri and supported his interpretation of the inclusions. Von Wasmann strongly refuted the contention of those investigators who did not accept the parasitic theory. Salmon (1897), London (1898), and later Boll (1903), regarded the inclusions as in part incorporated leukocytes. Babes maintained that they are extruded nucleoli. Ferroni and Massari considered them centrosomes. Huckel (1898) recognized the specific nature of the vaccine bodies but doubted that they represent parasites. He interpreted them rather to be a type of protoplasmic degeneration induced by a hypothetical vaccinal poison.

As opposed to these opinions, von Wasmann concluded that the vaccine bodies are the only structures characteristic of variola and vaccinia, to be found in the lesions of the skin and the mucous membranes in these diseases. They are absent in normal skin, and in skin

injured in ways other than by the virus (numerous unsuccessful attempts had been made to reproduce identical bodies by various means)

He emphasized that whenever active lymph is placed in an epithelial abrasion of the rabbit's cornea vaccine bodies appear, under other conditions they are absent. The rapid appearance of these bodies in an avascular tissue (cornea) in the absence of inflammatory cells excludes the possibility of their origin from leukocytes. He refuted their alleged origin from epithelial cell nuclei, because of their occurrence within apparently normal cells and cells dividing by mitosis. Their origin from cell protoplasm as a result of a specific toxic action (Huckel) he held was not proved, nor disproved, but seemed improbable, because no toxic effect from vaccine lymph filtered free of virus, had been demonstrated, and because the inclusions occur in dividing cells possessing normal protoplasmic radiations.

Councilman, Magrath and Binkerhoff (1904) were convinced of the parasitic nature of Guarnieri bodies, and Calkins (1904) in collaboration with them described in detail a complicated life cycle of the parasite, represented in the pleomorphism of the inclusions, which he classified with the *Sporozoa*. Tyzzer (1904) was likewise convinced of the parasitic nature of vaccine bodies.

After several ineffectual attempts on the part of other investigators, Negri (1905) succeeded in filtering the virus of vaccinia through Berkefeld candles IV and V, by using fresh cow lymph which had macerated several days in water at icebox temperature. Chamberland filters were impervious to the virus.

Negri emphasized that his results were not in any way to be construed as proof against the theory that Guarnieri bodies are parasites, for it might well be that in the developmental stages of such an organism filterable phases might occur. His experiments were confirmed by Remlinger and Osman Nouii (1905).

Paschen (1906) regarded the Guarnieri bodies as a manifestation of a specific alteration of cellular material, possibly through a reaction of the cell to an invading virus, but as not the virus itself. He postulates that vaccine virus is present in vaccine lymph in enormous amounts (dilutions of 1-1000 remaining active [Prowazek]), and that it must be exceedingly small, perhaps on the border of visibility. He admits that the virus might be incorporated in an invisible form within the vaccine bodies. On staining dilute vaccine lymph from children by Giemsa's method, Paschen could demonstrate enormous numbers of very minute granules which stained uniformly. Some of them appeared split in the middle and connected by a delicate thread. No conclusions were drawn as to the nature of these bodies, although at present Paschen regards them as the etiologic agent of vaccinia (personal communication to the author). Similar bodies were demonstrated within

the cells of vaccinal lesions by von Prowazek (1906) In 1908, Paschen reported the demonstration of the minute bodies in smears from variolous lesions They could be demonstrated especially well in preparations stained by Loeffler's flagella method

In 1909, Volpino described within epithelial cells of vaccinal lesions innumerable minute bodies exhibiting rapid movement The bodies were extremely small and their motions were of different kinds Sometimes they were simple, swift, oscillatory motions, again the movement was progressive from one point of the cell to another, so swift now and then that the moving body could no longer be accurately distinguished At times masses of the bodies moved together from one point to another and slow changes in form and position of such groups could be seen as a result of the motion of individual constituent granules Disintegration and rebuilding of masses of granules could be discerned as a result of separation or adhesion of individual granules with others

These motions were considered by Volpino to be a vital phenomenon, they could be seen in cells from ten to twelve days after their removal from the host, which he believed ruled out plasma streams, for the cells were disintegrated Von Prowazek thought the phenomenon represented merely Brownian motion Volpino mentions that Casagrandi and Bormann had confirmed his observations

More recently (1922) MacCallum and Oppenheimer have devised a method of separating similar extremely minute bodies in enormous numbers from vaccine lymph by the process of centrifugalizing a suspension of the virus in a fluid with a suitably adjusted specific gravity They have found that active virus is associated with the minute bodies and is entirely absent from the fluid which is free of them Lately (1926) Ciacini and Oppenheimer claim to have succeeded in cultivating the vaccinia granules in vitro with embryonic tissues

Cowdry (1922) was unable to confirm the observations of MacCallum and Oppenheimer completely By means of supravital staining he has derived evidence which convinces him that the Guarnieri bodies represent a reaction of the cell to the virus, consisting in an increase in the production of a cytoplasmic material which is normally present in minute quantities

#### SHEEP-POX

Sheep-pox is a very infectious disease characterized by a nodular eruption particularly in the skin, lungs, liver and kidneys According to Borrel, mesodermal cells are first affected and later there is an accompanying hyperplasia of epithelial cells of the tissue affected The period of epithelial proliferation in sheep-pox is much longer than in vaccinia, and cellular destruction is less rapid Virus is present in quantities within the nodules, and rarely demonstrable in the blood stream

In 1901, Bosc described inclusions within the cells of the nodules, both mesodermal and epithelial, which simulate those of variola and vaccinia. He considered them to be protozoan parasites. The lesions were studied carefully by Boirel in 1903. The presence of intracytoplasmic inclusions was confirmed, but he at that time interpreted them to be due to penetration of the cells by polymorphonuclear leukocytes which degenerated there. Later he considered them, as he did vaccine bodies, to be the product of a reaction of the cell to the invasion of the virus. Boirel saw in certain cells of the lesions minute bodies measuring about one fourth of a micron in diameter, round, sharply circumscribed, arranged singly and in pairs and in chains. He cautiously suggested that these bodies might be the virus. Later, in smear preparations stained by Loeffler's flagella method, he was able to demonstrate similar extremely minute granules in enormous numbers (Lipschutz). Likewise Paschen could demonstrate such granules in smears stained by Giemsa or Loeffler's Method (Lipschutz). They appeared similar to the granules previously found in smears from the lesions of variola and vaccinia. No one has as yet described motile granules in fresh preparations.

In 1903, Boirel succeeded in filtering the virus of sheep-pox through Chamberland candles of greater porosity than the ordinary or F filter, which was impervious to it.

#### MOLLUSCUM CONTAGIOSUM

The large hyaline, oval or elliptical structures which characteristically occur in or partially replace the superficial epithelial cells of the lesion of molluscum contagiosum, and which are now known as "molluscum bodies," were first described by Henderson in 1841. This was really the beginning of the study of cellular inclusions in relation to the etiology of virus diseases. Henderson regarded the bodies as parasites. In 1865, Virchow confirmed the observations of Henderson relative to the presence of molluscum bodies but considered them to be the result of a special kind of degeneration of the epidermal elements. Retzius successfully inoculated the disease on man in 1871, using material from the lesion for the inoculum, thus proving the infectious nature of the disease and demonstrating the virus content of the local lesion.

Juliusberg (1905) filtered the virus through Chamberland candles, successfully inoculating a human being with the filtrate. The filtrability of the virus was confirmed by Seria and thereafter by Wile and Kingery (1919).

The superficial nodules which constitute the lesion of molluscum have been shown by numerous investigators to consist of a local hyper-

plasia of cutaneous epithelial cells with little or no evidences of inflammation (Lipschutz, Goodpasture) The epithelial cells become greatly enlarged, especially those situated peripherally The typical molluscum bodies occupy the most superficial zone, while the layer beneath them is composed of greatly enlarged cells, which show profound structural changes gradually leading to the transformation of their content into the typical molluscum bodies Neisser considered these structures to be protozoa and similar to coccidia In opposition to the parasitic view, Hansemann, MacCallum, Unna, Benda and others held that they represent a peculiar sort of cellular degeneration The later view of von Prowazek, Lipschutz and Hartmann is that they arise as the result

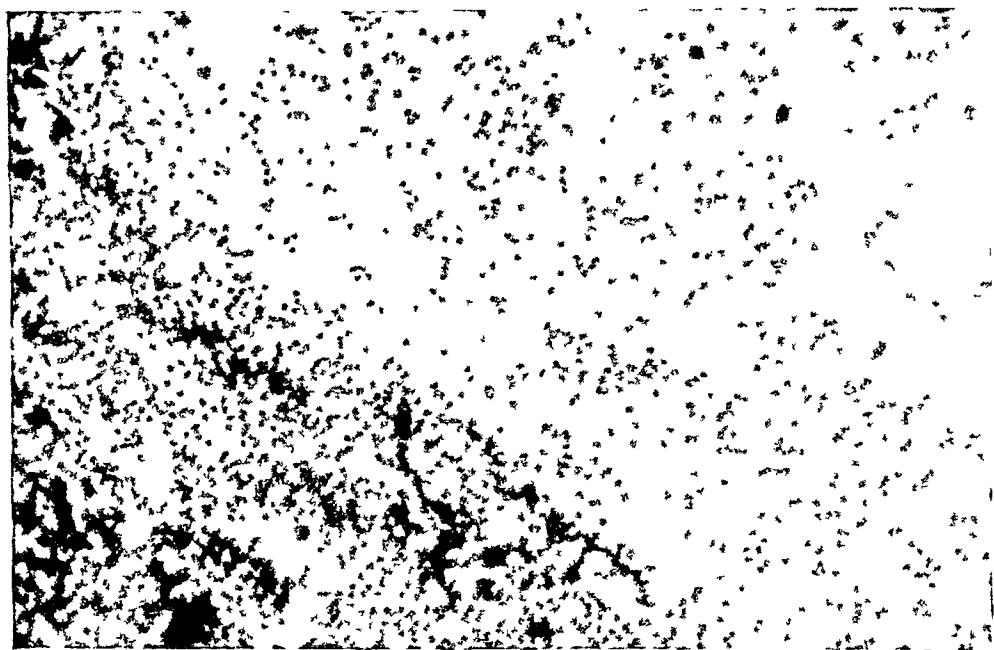


Fig 1—Smear from a lesion of molluscum contagiosum showing the Lipschütz bodies which compose the typical inclusions Stain used, carbol-aniline-fuchsin,  $\times 2000$

of a specific reaction on the part of epithelial cells to the invasion of the virus The virus itself, according to the investigations of Lipschutz (1907), is visible and consists of minute, round, dividing bodies measuring about one fourth of a micron in diameter, which can be demonstrated in enormous numbers in fresh preparations, and in smears stained by Giemsa's stain and by Loeffler's flagella method Lipschutz, by means of tissue sections, demonstrated these granules within the affected cells, almost filling them They appeared in the form of compact zooglyphic masses, separated into compartments, and were found only within cells Other larger bodies of irregular size and possessing a different affinity for stains were also observed in the cytoplasm

corresponding to similar structures, described by Benda, in the cells of fowl-pox lesions

Da Rocha-Lima concluded that the minute bodies of Lipschutz differ from known granular elements of the protoplasm, as for example, microsomes, Altmann's granules and mitochondria. Nor are they the result of coagulation from processes of fixation, for they can be seen with great clearness in cells in the fresh condition. In fresh preparations he found the elementary bodies in compact masses within the molluscum inclusions. Examined in water the epithelial cells became somewhat swollen and then he could observe the most active molecular movement. Often, still exhibiting great activity, the small bodies would leave the cell. This molecular activity I have confirmed in observing molluscum cells suspended in physiologic sodium chloride solution at room temperature. With high magnification and ordinary illumination a most active agitation can be seen within the intracellular masses. By light compression small bits of the granular material can be squeezed from the cell. The granules remain stuck together by a transparent jelly-like material in which their active movement causes a great agitation. There was no obvious swelling of the masses when suspended in distilled water. Within cells which had been kept in saline solution in the icebox for two weeks, groups of the intracellular granules could still be seen in active motion.

Sanfelice (1918) concluded from his study of molluscum bodies that they are not parasitic but have their origin in degenerative changes, which begin in the nucleus. According to his idea, nucleoli become extruded into the cytoplasm where they are transformed into the granular masses described by Lipschutz. Lipschutz admitted a nuclear origin for the so-called Benda bodies, but recognized no genetic relation between them and the elementary bodies which constitute the main structure of the molluscum inclusions.

More recently Goodpasture (1927) maintained that the hyaline oval masses which constitute the molluscum bodies of Henderson are formed by a coalescence of the masses of intracellular granules and other intracytoplasmic material. This is brought about by desiccation as the cells are forced outward. They are not formed, in his opinion, by a sort of keratinization as suggested by Lipschutz. It further appears to him that the minute bodies, the elementary bodies of Lipschutz, are not derived from extruded nucleoli, nor from any formed cytoplasmic constituent, but are morphologically consistent with a living, filter-passing, micro-organism. They develop about and within cytoplasmic vacuoles which may be regarded as the cellular response to the presence of a living foreign body. Finally, he is of the opinion that the elementary bodies of Lipschutz are the etiologic agent of the disease.

## FOWL-POX

Although one may find the statement still made that molluscum contagiosum of man and fowl-pox are the same disease manifested in different animals, there is no evidence for this beyond a certain similarity in form and manner of evolution of the lesions, and a very striking likeness in the changes which affected epithelial cells present. It has not been shown that the virus of either disease is cross-inoculable.

Fowl-pox is a specific eruptive disease of birds characterized by wart-like epithelial nodules which appear particularly on the unfeathered parts of the body and most typically about the head in spontaneous infections. The nodules consist of an epithelial hyperplasia, with little

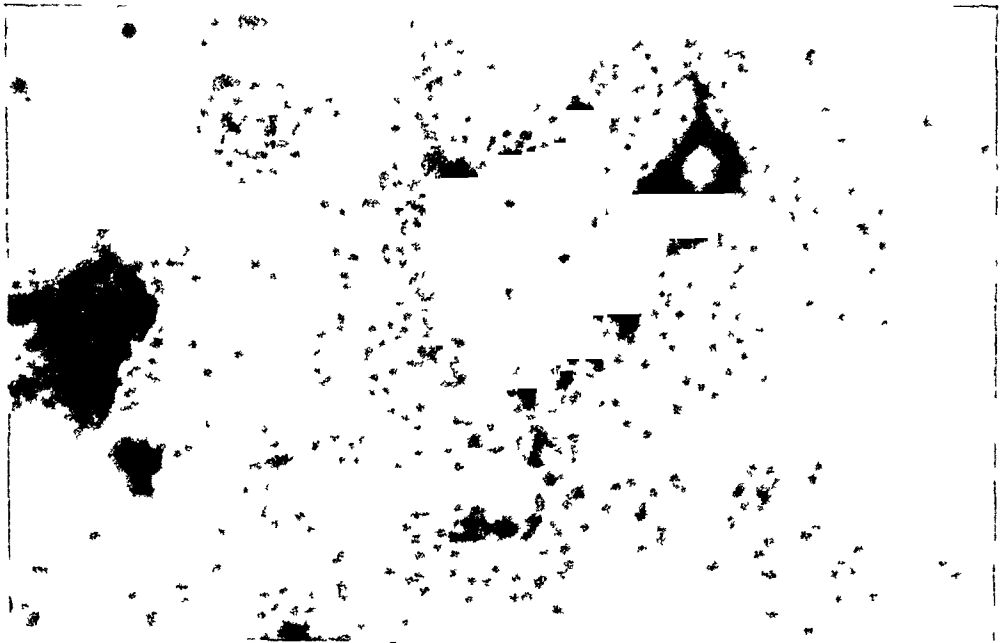


Fig 2—Smear from a fowl-pox lesion showing an inclusion broken up into its constituent Borrel bodies. Stain used, carbol-anilin-fuchsin,  $\times 2000$

or no inflammation in the underlying corium in early stages. Similar lesions may occur also in the mucous membranes, which are lined by stratified epithelium. In the course of from three to five weeks immunity is acquired and the lesions become dry and encrusted. They are eventually separated by an acute inflammatory exudate beneath.

The specific cellular inclusions seem to have been first described by Rivolta in 1869. They are round, hyaline, refractive masses situated exclusively within the cytoplasm. Often they attain a size larger than that of the nucleus of the same cell. Rivolta believed them to be parasitic and classed them with the *Giegarina*. The parasitic theory was maintained by Mingazzini, Sanfelice and others. Polowinkin,



Apolant, and lately Ludford and Findlay have considered the inclusions to be the result of cellular degeneration. Michaelis (1903) observed that they give reactions for fat with scarlet red and with osmic acid. Apolant found bodies in the affected cells which he considered to be extruded nuclear particles, but the fowl-pox inclusions proper, he thought, have an entirely cytoplasmic origin.

In 1902, Maix and Sticker succeeded in filtering the virus through Berkefeldt candles, but found it to be held back by the Chamberland F filter. They therefore disregarded the structures previously described as etiologic agents and definitely placed the virus among the filter-passers.

Borrel introduced a new morphologic conception of the virus of fowl-pox and other pox-like diseases when he discovered (1904) in smears from the lesion, stained by Loeffler's flagella method, myriads

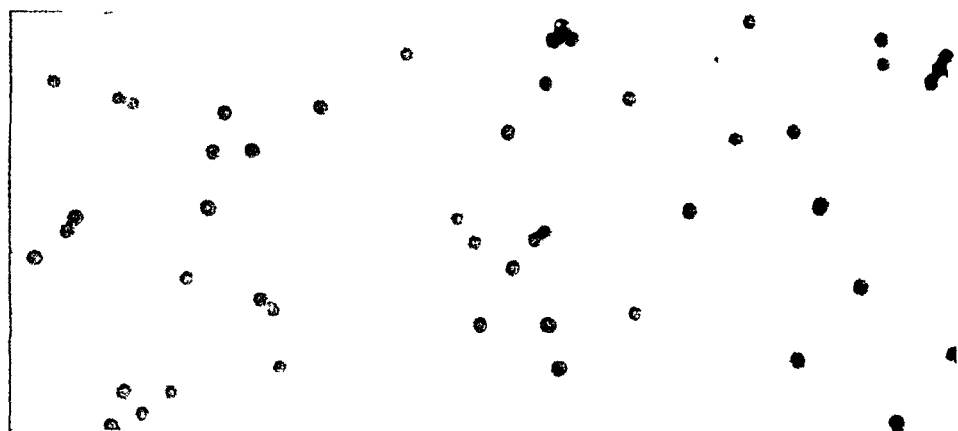


Fig 3—Smear from a culture of *Staphylococcus aureus*, stained and magnified the same as the smears in figures 1 and 2, for comparison. The photomicrographs were taken from smears prepared all in the same way. They were made with panchromatic plates and a B filter.

of minute ( $\frac{1}{4}$  micron), uniform, coccoid bodies arranged singly, in pairs, and in short chains. That these small structures, more diminutive than any known bacteria, represent the virus of fowl-pox, was accepted by Burnet, Lipschutz, von Prowazek and others. Burnet considered three hypotheses possible in explanation of the large cytoplasmic inclusions, namely (1) they are parasitic, (2) they are the products of secretion or degeneration of the cell brought about through the action of the unknown virus, (3) they enclose, enveloped in a substance of cellular secretion or degeneration, a micro-organism, whose form accords with the acquired facts of abundance and filtrability of the virus. Burnet's own investigations led him to adopt the last hypothesis. The enormous numbers of the micrococci, which he considered the

Borrel bodies to be, accords, in his opinion, with the extraordinary abundance of the virus. The fact that they occur in masses might account for the difficulty with which they are filtered, and perhaps for the unusual resistance to various external conditions which is characteristic of the virus. Loewenthal, however, still considered the inclusions typical of this and related diseases to be the product of cellular reaction, and Sanfelice, abandoning his idea of a blastomycotic etiology, discarded entirely the parasitic theory and supposed the disease to be due to a nonliving toxic substance which is reproduced as a result of the cellular injury which it induces. The inclusions are, accordingly, only manifestations of a degenerative change within the injured cells.

Recently it was shown by Goodpasture (1928) that the inclusions of fowl-pox can be easily removed from the cells, and when suspended in saline solution they appear as compact, hyaline, refractive bodies. When washed and suspended in distilled water they can be observed to swell rapidly becoming transformed into a number of globular compartments which tend to coalesce. After the swelling has continued for from one-half to one hour and the globules have reached a considerable size one can see, with the oil immersion lens and ordinary illumination, an extremely rapid agitation taking place within the globule. On careful observation it can be seen that this motion is due to the vibration of great numbers of minute uniform bodies, which are considered to be identical with the granules of Borrel, and the etiologic agent of the disease. When the swollen bodies are returned to saline solution they rapidly shrink through the loss of water and again become dense and hyaline. If a single large inclusion be crushed or smeared on a slide and suitably stained,<sup>1</sup> the minute bodies are clearly demonstrated incorporated by a hyaline matrix, which does not have the appearance of microbial capsules which have coalesced, but that of a more independent and voluminous material in which the granules are actually suspended.

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1 The minute bodies of fowl-pox and of molluscum contagiosum can be clearly demonstrated by staining a thin smear from a lesion in the following manner:

Dry the smear and fix by gently heating in a flame.

- (1) Mordant for one minute in  $\frac{1}{4}$  per cent potassium permanganate
- (2) Wash thoroughly in water
- (3) Stain for one minute in the following solution:

Alcohol 30 per cent	100 cc
Basic fuchsin	1 Gm
Phenol (crystalline)	1 cc
Aniline oil	1 cc

- (4) Wash thoroughly in water

- (5) Blot and dry. Observe with oil immersion objective.

## THE CHLAMYDOZOAN HYPOTHESIS OF VON PROWAZEK

The cellular changes associated with virus diseases, particularly the structure and composition of specific cellular inclusions, have been most thoroughly and minutely studied in relation to the aforementioned group of animal poxes. It has been found that there are intracellular inclusions specific for and more or less characteristic of each. Therefore any hypothetical consideration of the nature and significance of the inclusions of virus diseases in general must be based largely on the facts established for variola, vaccinia, sheep-pox, fowl-pox and molluscum contagiosum. There is a certain similarity in the gross lesions and in the characteristics of the inclusions typical of each of these diseases, and in addition to the larger intracellular masses which are designated as the "inclusions" proper, there have been found, by means of smears, stained sections, or by the examination of fresh material, very minute structures, coccoid in form, abundant in number, uniform in size and intracellular. These have been regarded by several investigators as diminutive parasites and the etiologic agents of these diseases. The granules are so small (0.1 to 0.25 micron) that it has not been possible to detect much difference in their morphology in these various infections. It is stated that the bodies are filtrable (da Rocha-Lima), that vaccine inoculum free of them is inactive, and that they may be cultivated in symbiosis with tissue cells (Ciaciun, Oppenheimer). Morphologic evidence of division has been found in the form of diplococcal and dumb-bell arrangements.

Any plausible theoretical interpretation of the inclusions therefore should include a consideration also of the minute bodies with which they are associated in the diseases mentioned. Three possibilities have been suggested in the literature:

- (1) That the inclusions represent stages in the life-cycle of a protozoan parasite, and certain of the minute bodies are of the nature of sporozoites (Calkins)
- (2) That the minute bodies are the virus, they invade the cell, injure it, and as a result of its consequent altered activity or actual degeneration the inclusions are formed, from the cellular material (Paschen)
- (3) That the minute bodies are the virus which penetrate the cell. The cell responds by forming a plastic material, which collects about the virus, partially or completely mantling it. The resulting product of the cellular reaction together with the incorporated virus constitutes the inclusion (von Prowazek, Lipschutz, da Rocha-Lima)

The third point of view is that on which von Prowazek constructed his hypothesis of *Chlamydozoa*, (mantled organisms), minute, filter-

passing micro-organisms which invade cells and irritate or kill them, thus giving rise, together with various inflammatory phenomena, to the lesions of the disease concerned. On the basis that it is unessential for all viruses of this type to stimulate or injure the invaded cell in such a way that it must react by the formation of an enveloping substance (a mantle), Lipschutz stressed the actual visible form of those minute bodies which he considered to be the real infective agents, rather than the hypothetic cellular response which may or may not be present. He therefore prefers to designate these viruses *Strongyloplasms* (rounded bits of living material).

More recent investigations of the diseases under consideration have not all substantiated the *Chlamydozoa-Strongyloplasm* theory. The observations of Gins on vaccinia (1922) were altogether confirmatory of this hypothesis, while Cowdry (1922), working with vaccinia and employing the method of supravital staining, concluded that the Guarnieri bodies are formed as a result of stimulation of the cells to produce in abundance a material traces of which he found in the same type of cell (corneal epithelium) under normal conditions. Ludford and Findlay (1926) investigating the cellular changes in the lesions of fowl-pox describe the development of Bollinger bodies and consider them to be the result of a reaction of the cell to the virus. They suggest that the bodies may in part be composed of a keratinoid material. Goodpasture (1927) on the other hand in a cytologic study of molluscum contagiosum confirms the observations of Lipschutz, von Prowazek and da Rocha-Lima, as to the presence of the minute components of the inclusions, denominated by Lipschutz, *Strongyloplasma hominis*. Also he finds (1928) in the structure of the inclusions of fowl-pox a most complete substantiation of von Prowazek's hypothesis of *Chlamydozoa*, in that these inclusions are composed of myriads of minute (0.2 micron) bodies suspended in a homogeneous matrix. This matrix may, he thinks, be a product of the micro-organism.

#### INTRACELLULAR PARASITISM IN VIRUS DISEASES

It seems to be generally accepted that viruses in general are multiplied locally in the specific lesions which they induce, and that there is an intimate relation between the cells affected and the particular virus concerned. The chlamydozoan hypothesis includes the conception of an invasion of cells by virus and implies an active proliferation of minute organisms intracellularly, although it does not exclude an extracellular multiplication. The rupture or destruction of cells would liberate the strongyloplasms which might invade other cells.

Certain investigators, while considering the inclusions to be due to reactive or degenerative changes, seem to believe also that virus actually invades the affected cells and that the alterations observed are due

to the presence of virus intracellularly. Thus Ludford and Findlay, referring to lesions of fowl-pox, state that "the earliest indication of infection of an epidermal cell is the formation of a small vacuole", and that "the disorganization of the cells incident upon keratinization possibly provides conditions for the virus to develop". It appears that the idea of an intracellular parasitism by viruses is more widely applicable to the facts than is the chlamydozoan hypothesis alone.

The suggestion of an intracellular multiplication of viruses has been made on numerous occasions but has not received the attention it deserves. In view of the known facts, it seems to me that a conception of an exclusively intracellular multiplication of virus would be applicable to infections by the etiologic agents of variola, vaccinia, sheep-pox, fowl-pox and molluscum contagiosum, and to those also of herpes and rabies, though morphologic data indicative of a micro-organism as the active agent in the last two is not convincing. In none of these diseases is there evidence of a proliferation of the virus in the blood or body fluids alone. Fowl-pox excepted, virus has not been demonstrated in the blood stream during these infections with any frequency. If virus multiplied in the body fluids independently of cells, it would seem almost certainly cultivatable on nonliving mediums. The filtrable agent of pleuropneumonia of cattle apparently proliferates within the pleural exudate, and no observations have been made which connect this micro-organism intimately with a certain type or group of cells as has been uniformly the case with the other viruses under consideration. The agent of pleuropneumonia is a filter-passing micro-organism which is cultivatable on nonliving mediums (Nocard and Roux).

Many viruses are prone to affect particular types of cells. This fact is emphasized in the use of the expression tropism in reference to certain viruses. Thus the viruses of vaccinia, fowl-pox and molluscum contagiosum are said to be epidermotropic, while those of rabies and poliomyelitis are neurotropic in the same sense. The selectivity of certain viruses for particular cells of the host is one of their most striking attributes, and the idea of an exclusively intracellular growth would be consonant with this important fact.

In this connection it has recently been stated that the quantity of active virus in herpetic lesions of the rabbit's cornea is proportionate to the number of cells containing the characteristic inclusions (Good-pasture), and the suggestion has been offered, with experimental evidence in support of it, that herpes virus is transmitted from a peripheral focus of infection to the central nervous system by its active multiplication within the axis-cylinders of nerves supplying the infected focus. It seems probable also that the viruses of rabies and poliomyelitis may be propagated in the same way, the conception being that these viruses

are essentially intracellular parasites and may find a suitable environment for proliferation within the cytoplasmic processes of nerve cells

The lesions of the poxlike diseases of animals consist of a hyperplasia of cells to a greater or less degree, together with various degenerative changes. It has been observed that in the lesions of some of them (variola, vaccinia, fowl-pox) mitosis may take place in cells which contain specific inclusions. On the assumption that the inclusions are a manifestation of the local presence of virus it would be logical to assume that such a division would give rise to two infected cells, thus spreading the virus without the necessity of repeated cellular invasion. This is of theoretical interest in connection with those virus diseases which are characterized particularly by cellular proliferation, such as Rous's sarcoma. Lately Borrel described a specific substance situated intracellularly and extracellularly, in Rous's sarcoma. It is suggested that this substance may be formed primarily within the cells and subsequently discharged into the surrounding medium.

#### SUMMARY

A review of the literature on virus inclusions discloses little uniformity of opinion relative to their composition and significance. The group of animal poxes (variola, vaccinia, sheep-pox, fowl-pox, molluscum contagiosum) presents morphologic evidence, which is lacking or inadequate in practically all other virus diseases, that the infective agent is a minute, rounded, uniform, micro-organism presumably capable of invading cells and of growing intracellularly. According to this conception, in its intracellular situation it induces the changes characteristic of the infection. These changes may be either an irritative hyperplasia, or a swelling, degeneration and necrosis. In molluscum contagiosum and fowl-pox, at least, there is evidence that the cytoplasmic inclusions peculiar to these infections are composed of masses of these small bodies suspended in a hyaline matrix which is either the product of the cell or of the virus itself.

A reviewer of the subject of filtrable viruses cannot but feel regret that the term filtrable has come to be the only term used as definitive of this group of pathogenic agents. He feels it would be of greater value to emphasize other characteristics of such agents which represent their activities and the effects which they induce, rather than to hold tenaciously only to an expression of a single physical characteristic which has become more or less trite. He would like to see some limit placed on the misuse of this group as a repository for all sorts of nondescript and ill defined conditions of unknown etiology and indefinite pathology.

It would seem to be a better practice to exclude from the group of filtrable viruses, or to hold in sub judice, those hypothetical agencies

which have not been filtered, which have not been shown to become reproduced at the site of the specific lesion which they cause, and which have not been demonstrated to induce important changes of form or function in the cells on which they exert their specific action and with which they appear to be in some way intimately related

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## Notes and News

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**University News, Promotions, Resignations and Appointments**—The following fellowships in medicine have been awarded by the National Research Council: Leon H. Collins, Jr., biochemistry and pathology at the University of Pennsylvania, Herbert L. Ratcliffe, parasitology at the Johns Hopkins University, P. Arthur Delaney, pathology at the University of Chicago, Eugene C. Woodruff, pathology at Vanderbilt University.

Kenneth C. Waddell, assistant professor of pathology, Albany Medical College, has resigned to accept an appointment in the medical service of the Presbyterian Board of Foreign Missions, in Brazil.

At Albany Medical College, Charles M. Carpenter has been appointed research fellow in bacteriology, Ruth M. Boak, instructor in bacteriology and assistant bacteriologist to the Albany Hospital, Yvonne de la Pasture, instructor in pathology and resident pathologist to the Albany Hospital, and Charles E. Martin, assistant in pathology.

George J. Rukstinat, Eustace L. Benjamin, Samuel A. Levinson, Chester C. Guy, Francis D. Gunn, Hamilton R. Fishback and Paul G. F. Schmitt have been appointed coroner's physicians of Cook County (Chicago) by Dr. Herman N. Bundesen, the first physician to be coroner in Cook County in sixty-five years.

Thomas B. Haslan has been appointed associate professor of pathology at Baylor University, Dallas, Texas, and medical director of the Baylor Hospital Clinic.

At Stanford University, Claus W. Jungeblut has been promoted from assistant professor of bacteriology to associate professor for five years.

It is reported that Werner Gerlach, Hamburg, has been appointed professor of pathology in the University of Halle.

At the University of Kansas, Raymond F. Gard has been appointed instructor in pathology and resident pathologist to the Bell Memorial Hospital.

At the Harvard Medical School, John Reginald Cuff has been appointed research fellow in pathology and John Archibald Ferguson, instructor in pathology.

**Ella Sachs Plotz Foundation**—According to the fifth annual report, twenty-one grants, totaling approximately \$12,000, were made during 1928. Twelve of these grants were made to scientists in countries outside the United States. In making grants, the trustees of the foundation favor researches directed toward the solution of problems in medicine and surgery or in branches of science bearing on medicine and surgery. Grants may be used for the purchase of apparatus and supplies needed for special investigations, and for the payment of unusual expenses incident to such investigations, including technical assistance, but not for providing apparatus or materials which ordinarily are part of laboratory equipment. Stipends for the support of investigators are granted only under exceptional circumstances. Applications for grants should be made before May 15, 1929, to Dr. Joseph C. Aub, 695 Huntington Ave., Boston.

**Fund for the Study of Influenza**—The Metropolitan Life Insurance Company has appropriated \$10,000.00 for the study of influenza by the company's influenza commission, of which M. J. Rosenau is chairman.

**Archives of Malignant Diseases**—The American College of Surgeons, Chicago, has appointed a committee to collect statistics bearing on the relation of heredity to human neoplasms. Dr. Bowman C. Crowell, 40 East Erie Street, Chicago, is the chairman of the committee.

# Abstracts from Current Literature

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## Experimental Pathology and Pathologic Physiology

DIABETES AND HYPERTHYROIDISM ELLIOT P JOSLIN and FRANK H LAHEY,  
Am J M Sc **176** 1, 1928

The analogy between diabetes and hyperthyroidism is emphasized and its importance in the interpretation of the symptoms, in the course of the disease and in the treatment is discussed. The patient with hyperthyroidism, from physiologic, pathologic and statistical evidence, is somewhat more prone to diabetes than other persons, and for the remainder of his life should be so regarded, whether operated on or not.

PEARL ZEEK

CARDIOVASCULAR FINDINGS IN WOMEN WITH SYPHILIS JOHN H ARNETT,  
Am J M Sc **176** 65, 1928

Two hundred and five female dispensary patients with tertiary syphilis, twenty-five with secondary syphilis and seventy-eight without this disease, as controls were subjected to a uniform examination, including, whenever possible, an electrocardiogram and an orthodiagram. Evidence was not found for the belief that, in the absence of definite evidences of cardiac impairment, syphilis by itself may produce cardiac enlargement. In 32 per cent of the tertiary group, a diagnosis of aortitis was made and in 2 per cent a diagnosis of aortic regurgitation. Arterial hypertension was slightly more common in the tertiary group, and arterial hypotension in the secondary group, than in the controls. T-wave defects were frequently noted in the tertiary group. Tachycardia was more common in both syphilitic groups than in the controls. Organic cardiovascular disease was not demonstrated in any of the patients with secondary syphilis.

PEARL ZEEK

NITROGEN ELIMINATION AND THE RESIDUAL NITROGEN FRACTION IN THE URINE ALLAN WINTER ROWE and BERNARD EMERSON PROCTOR, Am J M Sc **176** 103, 1928

In certain states of disease, that portion of the urinary nitrogen which remains after the urea, uric acid, ammonia and creatinine fractions have been deducted from the total definitely exceeds the limits characteristic of normal urine. In a series of cases including both normal persons, as controls, and patients with a variety of diseases, the amino-acid, hippuric acid and creatinine fractions were determined. While in cases showing high residuals there were increases in these constituents, the total left an undetermined fraction to be accounted for. Patients in whom the gonad and thyroid glands failed to function showed large increases in the creatinine output.

PEARL ZEEK

NITROGEN ELIMINATION AND THE SULPHUR PARTITION ALLAN WINTER ROWE and BERNARD EMERSON PROCTOR, Am J M Sc **176** 114, 1928

Further study of the nature of the residual nitrogen fraction in the urine reveals an increase in the neutral sulphur content in certain pathologic conditions above the level shown by the controls, but this increase is not commensurate with the observed increase in the undetermined nitrogen portion of the same urine. Therefore, it seems evident that in cases of high residual nitrogen fractions, the increase is due not only to a larger percentage of the known materials usually present in small amounts, but also to the appearance of some other nitrogen-containing material of unknown origin and composition.

PEARL ZEEK

THE CAPILLARY PRESSURE IN THE TOXEMIA OF PREGNANCY ISADORE MUFSON,  
Am J Obst & Gynec **15** 800, 1928

Mufson shows that there is not any characteristic morphologic picture to be found in the capillary bed corresponding with the normal or the clinical hypertension of pregnancy. The capillary pressure is, however, shown to be a definite prognostic indicator, when high, it proves to be unfavorable to mother and fetus. The capillary pressure following intravenous injection of magnesium sulphate shows a prompt reduction simultaneous with that of the brachial pressure, but the decrease is followed by a gradual return to the original reading.

A J KOBAK

INCREASE IN SUGAR METABOLISM BY THE OVARIAN HORMONE A M ESTES  
and W E BURGE, Am J Obst & Gynec **15** 847, 1928

The results reported are based on the rate of sugar absorption by paramecia as influenced by the addition of graded amounts of ovarian hormone. Washed paramecia were introduced into 500 cc of aerated lake water containing 500 mg of dextrose, and after thorough mixing this preparation was equally apportioned among five tubes. One tube was kept as a control and the rest received 25, 75, 100 and 200 mg of ovarian hormone, respectively. The sugar content was analyzed twelve hours later, and found to be more and more decreased with the greater amount of hormone up to the amount of 200 mg, with this amount it was found slightly decreased. This was assumed to have been due to a depressive action on the part of the large dose of hormone.

A J KOBAK

TOXICITY OF INTESTINAL CONTENTS IN HEALTH AND IN INTESTINAL OBSTRUCTION O H WANGENSTEEN and STANLEY S CHUNN, Arch Surg **16** 606, 1928

The content of the small intestines of several normal dogs and rabbits was injected intravenously, after Berkefeld filtration, into normal dogs and into the peritoneal cavity of rats. Also the intestinal content taken from above and from below the level of intestinal obstruction was similarly injected into normal animals. Of seventeen dogs thus receiving injections, two died, and in both of these the material injected was from the intestines of normal animals. All the dogs were ill with listlessness, vomiting, diarrhea, salivation, stupor and coma. Of thirty-six rats receiving the injections, eleven died. Nine of these had received injections of intestinal contents from below the point of obstruction. One died as a result of the injection of the normal content, and one as the result of the injection of material obtained from above the point of obstruction. Fifteen rats received injections of the intestinal content of normal rabbits, and five died. Of fifteen rats receiving injections of the content of the obstructed bowel, three died. When the material was not filtered through the Berkefeld filter, it caused death in a great percentage of the animals. From their experiments, the authors conclude that the normal intestinal content of both the dog and the rabbit is toxic on injection when submitted to the same treatment as the content of obstructed intestines. The material obtained from below the point of obstruction in dogs was even more toxic than the material obtained proximal to the obstruction.

N ENZER

CONTRACTION OF THE GALLBLADDER IN THE COMMON BULLHEAD (AMEIURUS NEBULOSIS) G M HIGGINS, Arch Surg **16** 1021, 1928

With proper aerating of the fish, it was possible to open the animal and observe the biliary tract and its response to the intraduodenal injection of cream and egg yolk. This injection elicited almost at once an active gastro-intestinal peristalsis and antiperistalsis. After about one hour and fifteen minutes, increased tonus in the gallbladder was apparent, this was followed by waves of contraction that emptied the contents into the common duct. The evidence points to an active

contraction of the muscle in the wall of the gallbladder, the degree of contraction varying according to the gastro-intestinal absorption of fat Duodenal peristalsis and intra-abdominal pressure are not factors in the discharge of bile from the gallbladder

N ENZER

THE METABOLISM OF LIVER TISSUE FROM RATS OF DIFFERENT AGES J A HAWKINS, J General Physiol **11** 645, 1928

A study of the respiration, aerobic glycolysis and anaerobic glycolysis of the livers of rats of various ages did not show differences for the first two processes In the livers of old and normal adult rats there was practically no anaerobic glycolytic activity, but there was some in the livers of very young rats This accords with the writer's view that the glycolytic activity of a tissue is a function of its rate of growth

H E EGGERS

CHANGES IN BLOOD DEXTROSE IN RABBITS AFTER INTRAVENOUS INJECTIONS OF HISTAMINE MAUD L MENTEN and HELEN M KRUGH, J Infect Dis **43** 117, 1928

The convulsions and anaphylactic shock produced by lethal doses of histamine in the rabbit may be accompanied either by no appreciable change in the blood dextrose or by a maximal hyperglycemia

The experiments reported indicate that allergy is not a factor in the production of agonal hyperglycemia

AUTHORS' SUMMARY

INSULIN OF THE PANCREAS FOLLOWING INTOXICATION OF RABBITS WITH PARATYPHOID B FILTRATE AND DYSENTERY BACILLI MAUD L MENTEN and HELEN M KRUGH, J Infect Dis **43** 121, 1928

Single intravenous sublethal injections of paratyphoid B filtrates do not appreciably alter the insulin content of the pancreas, as demonstrated by comparative biologic assays in test rabbits

The hypoglycemic potency of the insulin extract of the pancreas from rabbits in which injections of *B dysenteriae* (Shiga) had caused a prolonged fatal toxemia and hyperglycemia was slightly diminished

AUTHORS' SUMMARY

THE ASSOCIATION OF BOWEL DISEASE WITH VITAMIN C DEFICIENCY F P MACKIE and G D CHITRE, Indian J M Research **16** 77, 1928

Monkeys on a diet deficient in or lacking vitamin C become debilitated and anemic, lose weight rapidly and generally suffer from a terminal fatal dysentery Definite signs of scurvy appear in most of the animals This scorbutic condition can be checked by the administration of orange juice or by a return to a normal dietary, provided it is not advanced When once the scorbutic condition is well established, this treatment cannot be depended on to save the animals' lives The postmortem signs are most marked in the large intestine, which shows a succession of changes suggestive of local poisoning These signs vary from local congestion and thickening of the mucous membrane to a condition indistinguishable from ulcerating and sloughing dysentery The morbid histology suggests degenerative changes due to the action of a toxin, to which inflammatory changes are added secondarily Specific excitants of dysentery such as amebas or dysentery bacilli are not found in the large majority of cases The commoner fecal flora, in some cases, are found to have invaded the living tissues of the bowel wall, and this suggests that the toxic changes observed are the effect of such bacteria acting on tissues devitalized by the ill-balanced dietary These changes appeared in the alimentary canal in all animals kept on a diet deficient in vitamin C whether given infective sprue material or not Monilia were not found to have invaded the diseased areas, nor can the changes be attributed to their action A defective

dietary by itself powerfully predisposes to bowel derangements and acts probably by reducing the natural resistance of the intestinal epithelium to the invasion of bacteria or their toxins

AUTHORS' SUMMARY

STUDIES ON THE PHYSIOLOGY AND PATHOLOGY OF THE GASEOUS EXCHANGE  
IN THE TUBERCULOUS F POMPLUN, *Ztschr f Tuberk* **50** 387, 1928

The color of the blood is not an indication of the amount of oxygen absorbed. The oxygen values of the venous blood of patients with far advanced tuberculosis are decreased. This decrease is parallel with this calculated relative deficit of oxygen. The blood of patients with far advanced tuberculosis shows higher carbon dioxide values than the blood of those with less advanced tuberculosis. Low oxygen values are frequently found in the presence of high carbon dioxide values. Patients with artificial pneumothorax do not show any deviation from the normal. Analyses of arterial blood yielded essentially similar results. MAX PINNER

INFLUENCE OF THE THYROID ON THE REGENERATION OF CORNEAL EPITHELIUM  
M MINOWADA, *Acta Dermat* **11** 437, 1928

In thyroidectomized animals, epithelialization of the surface of the cornea is delayed as compared with the process in controls treated with thyroid substance.

DIFFERENTIAL DIAGNOSIS OF GLYCOSURIAS Y ÅKERREN, *Upsala Lakare Forh* **34** 341, 1928

In seven healthy or convalescent subjects, three patients with glycosuria who showed normal fasting blood sugar value from the start, and two patients with diabetes with remission, Åkerren found the fasting blood sugar value normal during and after a special diet consisting of the usual mixed diet with at least 400 Gm of bread and at least 100 Gm of sugar daily (the sugar in the usual food not included). He says that examination along these lines may be considered a function test of the carbohydrate metabolism of the organism. A patient with glycosuria who maintains a normal fasting blood sugar value under this forced carbohydrate intake shows complete carbohydrate tolerance and may be regarded essentially as a normal organism with respect to carbohydrate metabolism.

### Pathologic Anatomy

SPONTANEOUS HEART RUPTURE A B DAVENPORT, *Am J M Sc* **176** 62, 1928

Statistical data are given in reports of ninety-two cases of heart rupture collected from the literature and the following conclusions drawn. Spontaneous rupture of the heart is a disease of the aged, occurs most often on the anterior surface of the left ventricle and, in the aged, is practically always the result of coronary disease with infarction.

PEARL ZEEK

FREQUENCY AND DISTRIBUTION OF FOSSA PHARYNGEA IN HUMAN CRANIA  
HENRY B COLLINS, JR, *Am J Phys Anthropol* **11** 101, 1927

Human craniums to the number of 9,135 in the U S National Museum were examined, and the frequency of the fossa pharyngea noted. As to sex, the fossae were distributed as follows: females, 6.55 per cent, males, 4.98 per cent, children, both sexes, 5.35 per cent. The Melanesians show the highest frequency of the

fossa, the white races, the lowest Among American Indians the highest frequency is found among the Shoshoncan-speaking tribes, followed closely by the Sioux, Apache, and other Plains tribes, and the Aleutians The Eskimos show the lowest frequency of any American group

AUTHOR'S ABSTRACT

SEX DIFFERENCES IN THE PATHOLOGIC PICTURE OF SYPHILIS ALDRID SCOTT  
WARTHIN, Am J Syph **12** 301, 1928

In a summary of the differences in the pathologic changes of syphilis in the two sexes, the most striking facts presented are those bearing on the relatively greater immunity of the female to this infection than the male possesses This immunity is shown particularly in the case of the heart, aorta, central nervous system and ovary On the other hand, the pathologic lesions of latent syphilis in women are usually more extensive in the liver, pancreas, suprarenals and rectum than in men, but severe clinical forms of these visceral lesions are relatively infrequent when compared to the severe forms of cardiovascular syphilis and that of the central nervous system in man The general aspects of syphilis in the female, therefore, tend to be much milder than in the male Woman's relatively greater immunity to syphilis is most strikingly shown during the child-bearing period During this time she may not have any clinical symptoms of syphilis, and the Wassermann reaction may be negative Nevertheless, such an apparently normal woman may bring syphilitic children into the world, and the placenta, umbilical cord and fetal tissues of her progeny may show spirochetes in enormous numbers The production of a syphilitic child may be the only diagnostic fact that can be determined Not until the menopause approaches may signs of syphilitic lesions and a positive Wassermann reaction appear It is this aspect of syphilis that makes the problem of this disease of such tremendous sociologic importance Many reasons have been advanced in explanation of this immunity in women differences in the character of the serums in the two sexes, that of women having greater protective power against the spirochetes, greater degree of lymphocytosis, protective action of the thyroid and other endocrinal secretions in women, differences in habits of the two sexes, conceptional protection through chorionic proteins, etc The facts stand out, however, that in addition to a general modification of the disease as affecting the body as a whole, there is also in the woman a marked localized resistance to syphilis in certain organs and tissues It is difficult to explain the exemption of the ovary in any other way, when it is known that the male sex gland has an especial susceptibility to syphilitic injury It does not seem possible that evidences of syphilis in the ovary is being missed, it is much more reasonable to believe that syphilitic lesions do not occur in the ovary If they do, they must be totally different from those seen in other organs All in all, one can only surmise that there is some deep-seated biologic sex difference—a genetic, inherited, sex-limited resistance on the part of the ovary to the presence of the spirochete It might be that *Spirochaeta pallida* is a pathogenic descendant of some harmless spirochetal form inhabiting the female body ages ago, and that in consequence woman establishes a more comfortable partnership with this organism than does man Such a theory does not, however, explain a higher degree of immunity of the woman during the period of child-bearing, and the apparent increase of immunity as the result of conceptions Whatever may be the explanation of woman's relative immunity to this infection, whether one or several of these factors contribute to it, the important fact remains that syphilis manifests itself in the female almost as if she were another animal species

In regard to this sex-difference in reaction to infection with *Spirochaeta pallida*, there center not only grave sociologic problems but also the most difficult practical problems in the diagnosis and treatment of syphilis

AUTHOR'S SUMMARY

MASSIVE COLLAPSE (ATELECTASIS) ASSOCIATED WITH PULMONARY TUBERCULOSIS AND TUMOR EDWARD N PACKARD, Am Rev Tuberc **18** 7, 1928

Five cases are cited which exhibited the signs and symptoms of massive collapse, but in none of these did an operation precede the development of the atelectasis. Four of these patients had chronic pulmonary tuberculosis. One case was complicated by carcinoma, and one patient had a tumor of the lung. Autopsies in two of the cases showed that the collapse of lung tissue was due to bronchial obstruction. Massive collapse of the right lung may be one of the causes of acquired dextrocardia. Rapid, massive pulmonary fibrosis of a lobe or of the whole lung is probably etiologically a massive atelectasis.

H J CORPER

NODULAR GOITER WITH HYPERTHYROIDISM H M THOMAS, Arch Surg **16** 117, 1928

In thirty-two cases of nodular goiter presenting clinical symptoms of hyperthyroidism, sections revealed areas of hypertrophy and hyperplasia. A close parallelism can be traced between the degree of morphologic change and the severity of the symptoms. In this series of nodular goiters, the only difference between them and true exophthalmic goiter seems to be one of degree. The conclusions fit in with Rienhoff's hypothesis.

N ENZER

OBSTRUCTIVE MASSIVE ATELECTASIS OF THE LUNG P N CORYLLOS and G L BIRNBAUM, Arch Surg **16** 501, 1928

The authors offer this definition of the condition: "Obstructive massive atelectasis of the lung is a febrile complication which appears within a few days after operation, generally on the abdomen, and is always due to a more or less temporary but complete obstruction of the bronchus and followed by the more or less complete absorption of vesicular air in the corresponding portion of the lung, thus giving the organ the structure of a fetal lung. It is especially and often conclusively characterized by the clinical symptom of a unilateral, pulmonary consolidation with displacement of the mediastinum and the heart toward the affected side. The prognosis is generally favorable, and ends in lysis or crisis. The treatment is bronchoscopic aspiration of the obstructing mucus as early as possible."

N ENZER

ADENOMYOMA OF THE STOMACH J H WOOLSEY and R J MILLZNER, Arch Surg **16** 583, 1928

At operation for what was suspected to be a jejunal ulcer, a small ringlike thickening was found on the anterior surface of the pylorus. This was excised and examined. Grossly the mucosa was normal over the area of thickening, and the transverse section through it gave the picture of an old callous ulcer. Microscopic examination revealed intact, essentially normal mucosa, a thick, fibrous submucosa, and adenoma scattered throughout the submucosa and muscularis. The glands were of three types—more or less undifferentiated ones, glands resem-



bling pancreatic acini, and others resembling Brunner's glands. Between the glands were narrow strands of smooth muscle which more or less surrounded the alveoli.

The condition of adenomyoma of the stomach is undoubtedly a heterotopia developing from epithelial buds or diverticula, the commonest form of which is an accessory pancreas. One of the interesting statements in the article is that the alveoli open into ductlike structures, which eventually communicate with the lumen of the stomach. This is interesting because the reviewer made serial sections on two accessory pancreases found in the wall of the ileum, and was unable to find any communication with the lumen, although there were several distinct duct structures in the nodules. So far, the malignant degeneration of the tumors has not been described except in reports of three cases of accessory pancreas.

N ENZER

BLOOD IN THE CEREBROSPINAL FLUID, CLINICAL DATA C BAGLEY, Arch Surg **17** 39, 1928

The most interesting and important part of this paper lies in the report of twenty-seven cases in which bloody cerebrospinal fluid was present with various types of underlying lesions. Five of these patients had cerebral aneurysms. In the majority, the hemorrhage was due to trauma. The presence of blood in the spinal fluid constitutes a meningeal irritant, and the symptoms depend on the degree of hemorrhage. These may range from slight headache to severe convulsive seizures and loss of consciousness. The symptoms may subside as the blood is absorbed, but the irritation may be sufficiently severe to cause a connective tissue proliferation and blockage of the foramina.

N ENZER

FAT EMBOLISM, INCIDENCE AT POST MORTALITY E P LEHMAN and R F McNATTY, Arch Surg **17** 179, 1928

In a previous article (ARCH SURG **14** 621, 1927) the authors concluded that the fat found as embolism in nontraumatic cases probably appeared by the coalescence of the ultramicroscopic particles of fat normally appearing in the blood plasma. This coalescence was attributed to a breaking down of the physiologic emulsion from physical or chemical changes in the blood, and was produced experimentally in the living dog by the administration of ether. Because of the generally accepted observation that if fat embolism occurs it will be seen in the lung, the lungs of fifty unselected patients were examined for fat. Intracapillary globules of fat were diagnosed as fat embolism. Most of these were large enough to plug capillaries, and the degree of embolism was graded according to the amount found in a section. It seems possible that a source of free fat in the blood stream may be the distribution of fat-containing leukocytes. With one exception, wherever leukocytes were filled with fat, embolism also occurred. Definite fat embolism occurs in more than half of all lungs examined at autopsy. About half of the lungs in which fat embolism occurs are from patients in whom there has been no history of trauma. In a small proportion of cases in which definite trauma is recorded, emboli could not be found on a single examination. Fat embolism is found in an overwhelming proportion of lungs from patients subject to injury or operation. Fat embolism occurs in more than half of the miscellaneous diseases without history or trauma. The presence of fat embolism in the lung after trauma does not justify the conclusion that such fat has been caused by the trauma, or that it has caused death.

N ENZER

ARTERIOVENOUS ANEURYSM OF THE BRAIN W E DANDY, Arch Surg **17**  
190, 1928

Eight arteriovenous enurysms of the brain are presented, and twenty-two cases from the literature. Arteriovenous aneurysms of the brain are similar to those elsewhere in the body, except that traumatic arteriomenous aneurysms probably do not occur in the brain, because large arterial and venous trunks are not in apposition. There are two of these types of arteriovenous aneurysms, one in which an anomalous vessel of congenital origin establishes a direct end-to-end communication between an artery and vein, the other in which a network of vessels, a so-called angioma, is interposed between an artery and one or several veins. A capillary bed between the artery and vein is lacking in both types, the arterial blood passes directly into the veins. They constitute 1 per cent of a series of tumors of the brain. Hemorrhage was present in 40 per cent of these aneurysms.

N ENZER

ASCARIASIS OF THE GALLBLADDER CHARLES BRUCE MORTON, Arch Surg  
**17** 324, 1928

The literature was searched for reports of cases of ascariasis of the gallbladder. Seven cases were found, and five have been briefly summarized. A case of teniasis of the gallbladder was found and also summarized. It was similar in many respects to the cases of ascariasis. All cases had been diagnosed only after operation or necropsy. A case of ascariasis of the gallbladder which I encountered has been described, and the condition discussed in relation to its etiology, diagnosis and treatment. It was pointed out that the disease is rare and difficult to diagnose. Furthermore, the treatment is surgical, and cholecystectomy is probably the operation of choice. Anthelmintics are indicated for prophylactic and postoperative use. The history of ascariasis in a patient with signs of cholecystic disease should always suggest the possibility of ascariasis of the gallbladder.

AUTHOR'S SUMMARY

SIMPLE, NONSPECIFIC ULCER OF THE COLON M E BARRON, Arch Surg  
**17** 355, 1928

Those ulcers not due to any known specific cause are considered in this article. Fifty cases collected from the literature are reported in detail, and the author adds three cases from his own experience. The ulcers may be single or multiple, and may occur anywhere in the colon. Thirty-one of these ulcers were in the right portion of the colon. In this series, they were much more common in males. The diagnosis may be suspected from a history of persistent localized pain and with the aid of the x-rays. This may show a perforating defect or an encroachment on the lumen by a mass. This mass is inflammatory and must be carefully distinguished from malignant disease. The diagnosis is usually made after perforation when an exploratory operation is performed. Barron thinks that these ulcers should be classed with the peptic ulcers and are related to them by a common etiology.

N ENZER

"STREAM LINE" PHENOMENA IN THE PORTAL VEIN AND THE SELECTIVE DISTRIBUTION OF PORTAL BLOOD IN THE LIVER G H COPPER and B M DICK, Arch Surg **17** 408, 1928

By injecting trypan blue into the tributaries of the portal vein of dogs, the authors demonstrate that the site of its deposit in the liver will depend on the

vessels into which injection is made. Thus when injections of the dye were made into a vein on the lesser curvature of the stomach or into a branch of the splenic vein, it stained only the left half of the liver. The veins of the upper part of the duodenum, head of the pancreas and jejunum carried the dye to the right lateral lobes. Those from the colon distributed the dye to all parts of the liver, but more particularly to the large lobe on the left. By a process of transillumination of the portal vein, the authors were able to demonstrate that three streams of blood are present in that vein, and that they correspond to the drainage from the three regions previously mentioned. It would seem, therefore, that certain areas of the liver are supplied by blood from fairly well-defined intra-abdominal regions and that the blood from one region does not mingle with that from another either in the portal vein or in the liver.

N. ENZER

CARCINOMA OF THE ISLANDS OF THE PANCREAS. HYPERINSULINISM AND HYPOLYCEMIA. WILLIAM THALHIMER and FRANCIS D. MURPHY, J. A. M. A. **91** 89, 1928

After two and a half years of gradually increasing severity of symptoms, the patient developed a state of almost constant semistupor accompanied by frequent convulsions and marked hypoglycemia until death followed, apparently from exhaustion. At necropsy the only significant pathologic lesion found was a small primary tumor of the pancreas. Its microscopic appearance indicates that it originated from the cells of the islands of Langerhans, and that the tumor is either a carcinoma of a low grade of malignancy or else an adenoma. It is believed that the active secretion of insulin by these tumor cells caused a hyperinsulinism which resulted in hypoglycemia and, finally, in death.

AUTHORS' SUMMARY

RECOVERY OF HUMAN OVA FROM UTERINE TUBES. EDGAR ALLAN, J. P. PRATT, O. U. NEWALL and LELAND BLAND, J. A. M. A. **91** 1018, 1928

This report records the recovery of seven ova from the uterine tubes, among them one set of twins and one case of internal migration of an ovum from one ovary to the other tube. One ovum was recovered on the twelfth, four (including the twins) were recovered on the fifteenth and two were recovered on the sixteenth day of the menstrual cycle. The last two showed signs of degeneration, and further correlation of their condition with the histology of the corresponding corpora lutea may place their time of ovulation earlier in the cycle.

AUTHORS' SUMMARY

THE PATHOLOGY OF THE MEMBRANES OF BRAIN AND SPINAL CORD. THOR ROTHSTEIN, L. W. AVERY and R. RICHTER, J. Infect. Dis. **43** 1, 1928

The cells of the dura and of the pia-arachnoid form a syncytial membrane spinning through the whole thickness of the respective meninges, which demonstrates that the original mesenchymal syncytium remains permanent through life, so far as dura and pia are concerned. The so-called "membranes" of the meninges, instead of being only supporting structures, are protoplasm having the constituents for highly important functions.

The so-called surface endothelium forms an integral part of the syncytium and has fibroblastic characteristics.

Reticulum consist of protoplasm with cytoplasmic fibrillae. In the protoplasm which contains or accompanies the reticular fibers, mitochondria can be demonstrated. Fibroglia is formed from the cytoplasmic fibrillae, and collagenic fibers also arise from cytoplasmic fibrillae.

AUTHORS' SUMMARY

STUDIES ON SCURVY ARTHUR W MEYER and LEWIS MCCORMICK, Stanford University Press, 1928, pp 1071

THE SYMPTOMATOLOGY AND GROSS MORPHOLOGY OF EXPERIMENTAL SCURVY IN THE GUINEA-PIG ARTHUR W MEYER

As far as the gross lesions regarded as diagnostic of experimental scurvy in the guinea-pig are concerned, the author adds little except that the presence of fatty degeneration in the liver and absorption on the roots of the molar teeth, with the possibility of depressing the posterior or all of the molars, are constant morphologic signs. The extent of depression that is possible always is greatest in the last molars and decreases from back forward. Outwardly evident lesions in the bones and joints usually are absent in the mature guinea-pig, and such animals may show evident signs of pain without the presence of swollen or tender joints and without hemorrhage in the extremities. They also may be active and apparently unaffected and yet have extensive hemorrhages and may have suffered considerable absorption on the roots of the molars and in the alveoli. Some subcutaneous and muscular hemorrhage is almost always present somewhere at the time of autopsy, and duodenal, cecal and vesical (urinary) and paravesical hemorrhages are common. The stomach and, in fact, the entire intestinal canal, usually contains little food, and I have come to regard the lack of appetite and interest in food and also the lessened activity among the earliest signs of the existence of the scorbutic condition. An entire lack of interest in food always was an absolute indication of death within a few days no matter how well the animal seemed or how active it was. Increasing inactivity and weakness and increased loss in weight and appetite usually enabled one to forecast the approximate time of death except for the advent of sudden complications. The new observations on the gross pathologic condition of experimental scurvy in guinea-pigs here reported are the highly nervous condition of some of the animals, the recovery of health of young pigs after a condition of complete helplessness in the posterior half of the body, the occurrence of permanent locomotor disabilities, shortening of the roots of the teeth by absorption so that the molars can be depressed below the level of the gums, the occurrence of pronounced gaseous distention of the stomach in some animals, and pseudopneumonic lesions in the lungs of others, fatty change, even to whiteness, especially of the liver, to a lesser degree of the suprarenals, and microscopically also in other organs, as will appear in part II, necrotic areas in both liver and suprarenals, degenerative changes in and fibrosis of the costal cartilages even in regions remote from the costochondral junctions.

THE MINUTE MORPHOLOGY OF EXPERIMENTAL SCURVY IN THE GUINEA-PIG ARTHUR W MEYER

Hemorrhages were noted rarely in the skin, almost universally somewhere in the subcutaneous tissues, commonly in the muscles, the urinary bladder, the periosteal, the periodontia, many glandular organs, and the lungs, stomach and intestine. They were also seen in the gallbladder, the brain, spinal cord, posterior root ganglions and the nerve trunks. Intra-gingival and intra-articular hemorrhages were not observed. The marked fatty infiltration and degeneration evident grossly in the liver and sometimes also in the kidney were found present microscopically in the kidney, the suprarenal, and even in the lung and the peribronchial cartilages, the pancreas, some skeletal muscles, and the walls of a blood vessel. Degenerative changes other than fatty changes, resulting in the complete loss of substance, were observed in the cartilages, bones, teeth, muscles, many glandular organs and also in the central, the peripheral and the sympathetic nervous systems. This widely distributed liquefaction of the cytoplasm and cell walls results in destruction of cartilage cells and of the cartilaginous matrix, at least in the costal cartilages, in the detachment of the periosteal and periodontia, in reduction in the caliber of the bones, and in both the caliber and the length of the implanted portions of the teeth. It may effect not only the separation of ununited epiphyses and loosening of the teeth, but the complete destruction of the parenchyma of some areas in the glandular and other organs, in desquamation of the mucosa

and of renal epithelium, and in complete disintegration of the walls of blood vessels. In addition to the fatty and lytic changes, coagulative changes, such as extreme waxy degeneration in the muscles, were also noted in glandular and nervous tissues. The only proliferative changes noted occurred in the costal cartilages and concerned an increase in caliber at the region of the costochondral junctions and an invasion of connective tissue into areas of degeneration. Necrotic areas on the surface and in the substance of the liver were occasionally observed, but perhaps were wholly unrelated to scurvy. Vacuolation was common in many organs, and fenestration up to a marked degree was observed, especially in muscle, bone marrow, the pulp of the teeth, and also in the cord and brain.

#### SOME CHARACTERISTICS OF THE BLOOD OF THE GUINEA-PIG IN EXPERIMENTAL SCURVY LEWIS M. McCORMICK

Definite cytological changes occurred in the blood of guinea-pigs with experimental scurvy. These changes became evident after the pigs were on the author's scorbutic diet for ten days. They consist of a decrease in red blood cells, hemoglobin and color index, an "apparent" decrease in fragility, a relative decrease in the number of lymphocytes, an absolute increase in polymorphonuclears and an increase in reticulated and nucleated red blood cells and leukocytes. The eosinophil, basophil, monocyte and transitional cell counts were not considered characteristic of scurvy.

#### AUTHORS' SUMMARY

#### CONGENITAL ANEURYSM OF THE CEREBRAL ARTERIES F. GREEN, Quart J Med 21 419, 1928

From 1922 to 1927 at St. Bartholomew's Hospital, London, nineteen bodies at autopsy presented basal cerebral aneurysms, and in seventeen death was due to their rupture. Five of these were embolic and associated with malignant endocarditis, two were associated with extensive arteriosclerosis, and twelve were congenital. In three bodies two aneurysms were found, and in one three saccular dilatations were seen on various branches of the circle of Willis. The average age of death in the embolic type was 25 years, in the sclerotic type, 58 and in the congenital type, 43. The average age at death from lenticulostriate and pontile hemorrhage was 58 years. The three reports under consideration concerned a single woman, aged 30, who lived for six weeks with leakage from a saccular aneurysm of the right middle cerebral artery, a married woman, aged 49, who died two days after the onset of bleeding from an aneurysm identical with the foregoing one, and a man, aged 21, who had suffered repeated attacks of headache and loss of consciousness. Death occurred in the last patient fifteen hours after the last attack, and at autopsy three aneurysms were found associated with coarctation of the aortic isthmus, a bicuspid aortic valve and fenestrated mitral cusps. Histologically, the essential changes in the aneurysm walls were atrophy and connective tissue replacement of the media occurring frequently at a single point in the circumference and associated with splitting of the elastic lamina and subendothelial hyperplasia of the intima.

GEORGE RUKSTINAT

#### LIPOMA OF CEREBRIFORM TYPE A. BOTTO-MICCA, Gazz. d. Osp. 49 451, 1928

A rare type of lipoma in a married woman, aged 25, is reported by Botto-Micca. The case is interesting chiefly from the clinical side. The tumor, which was located on the back between the twelfth dorsal and the third lumbar vertebrae, consisted of a roundish yellow mass, about 10 cm. long, 7 cm. wide, and 1 cm. thick, with an oily serous excretion. When first discovered by the mother, when the daughter was 14, it had about the same size and appearance as shortly before the operation, eleven years later. Its peculiarity consisted in the fact

that it was composed of several dozen lobes, separated from each other by deep furrows, which gave to the mass the same appearance as the surface of the brain. At a distance of from 0.5 to 10 cm, there were a few isolated lobules. The patient recovered rapidly from the operation and when seen more than a year later was in excellent health, having gained 8 Kg. in weight.

HEALING PROCESSES IN PULMONARY TUBERCULOSIS P. HUEBSCHMANN, Beitr. z. Klin. d. Tuberk. **68** 718, 1928

Small apical lesions of the acinous type heal frequently by the formation of a thin fibrous scar which fits itself into the surrounding alveolar structure. The neighboring alveoli, which have lost their elastic fibers, are usually emphysematous. This is the reason that such processes may not leave any roentgenologic signs. The disappearance of other roentgenologic shadows is frequently due to the absorption of perifocal exudate. Larger bronchopneumonic foci may heal only by encapsulation and fibrous replacement of the caseous center.

MAX PINNER

THE ACTION OF CEMENT DUST ON THE LUNGS F. SCHOTT, Beitr. z. Klin. d. Tuberk. **69** 43, 1928

According to clinical and roentgenologic observations and experiments on rabbits, the following conclusions are reached. Inhalation of cement dust over a period of years may produce chronic catarrh, bronchitis and emphysema with alterations in the hilum. Actual disease does not occur before an exposure of at least ten years. Pneumoconiosis produced by cement is more benign than chalicosis, it does not favor the development of pulmonary tuberculosis.

MAX PINNER

THE DISTRIBUTION AND THE ORIGIN OF CONNECTIVE TISSUE IN PULMONARY TUBERCULOSIS A. SEGA, Beitr. z. Klin. d. Tuberk. **69** 403, 1928

Connective tissue is produced in the lung in three fundamentally different forms: (1) heavy and dense sclerosis with rich vascularization, (2) nodular fibrosis, and (3) annular fibrosis. The connective tissue arises from interalveolar septums and from the interlobular, subpleural, perivascular and peribronchial tissue. The genesis from interalveolar septums and from interlobular connective tissue occurs chiefly in annular and nodular fibrosis. The other types of origin lead chiefly to vascularized sclerosis.

MAX PINNER

AN UNUSUAL THYROID TUMOR W. ROTTER, Zentralbl. f. allg. Path. u. path. Anat. **42** 289, 1928

A woman, aged 41, had two masses the size of hen's eggs removed from the thyroid gland. Microscopically, these proved to be polymorphocellular sarcomas with spindle cells predominating. Scattered throughout were numerous adenomas and spots of necrosis. The lumens of the veins in the tumors were filled in many instances with sarcoma growths. Seven years later the woman broke her elbow and arm, and because of progressive swelling of the shoulder exarticulation was done. Gray-red tumor masses were found at the neck of the humerus and in the surrounding soft tissues. Microscopically, the tumor masses had the following components: colloid struma, adenoma, trabecular with solid cordlike strands, small and large epithelial collections, partly solid and partly cystic, papillary fibro-adenoma, cylindric cell carcinoma, squamous cell carcinoma with definite pearly formation, and spindle cell sarcoma. In accounting for the squamous cell elements, the author cites Kloppe, who saw such cell nests in the thyroid, and Wegelin, who saw squamous cell metaplasia in thyroid adenomas and the possibility of change in cell type in a metastasis.

GEORGE RUKSTINAT

MELANOTIC PIGMENTATION OF THE EPICARDIUM F MATZDORF, Centralbl f allg Path u path Anat **42** 294, 1928

The deposits were found in two patches varying in size from that of a linseed to that of a bean in the right ventricle in a man, aged 83, in multiple small dark-brown scale or shingle-like collections in the left ventricle in a woman, aged 59, and on the right ventricle of a man, aged 40. In the first and third instances, chromatophores were found in the endothelial layer of the epicardium and between it and the subepicardial fat tissue, in the second case, they were found between the epicardium and the muscle. According to the author, this is the first communication dealing with this pigment in the epicardium of man, but he points out the relative frequency of endocardial deposits in sheep in which a mixture of races has led to degenerative changes.

GLORGL RUKSTINAT

EXTENSIVE MYOCARDIAL NECROSIS FOLLOWING ILLUMINATING GAS POISONING H TESSERAUX, Centralbl f allg Path u path Anat **42** 344, 1928

A woman, aged 69 found unconscious from illuminating gas poisoning, was given metrazol and lobelin, artificial respiration by the Draeger apparatus and relieved of 350 cc of blood by venesection. Three days later she died, and at the autopsy there were found confluent bronchopneumonia of the left lower lobe, symmetrical gray-brown spots of softening in the globus pallidus and saggillations and petechial hemorrhages mingled with light yellow spots of necrosis in the left ventricle of the heart. Microscopically, the myocardium exhibited loss of nuclei and eosinophilic staining. Single muscle cells and bundles swollen and without cross-striations and in the yellow places medium sized fat droplets. Collections of polymorphonuclear leukocytes bordered such places. The blood vessel walls were everywhere normal, and bacteria were not seen in gram stains.

GEORGE RUKSTINAT

THE STRENGTH OF THE CAPILLARY WALL AND CAPILLARY HEMORRHAGES M VOLTERRA, Klin Wchnschr **7** 1464, 1928

The idea that the strength of the normal capillary is dependent on the endothelial cells does not rest on an anatomic basis. Fragility of the endothelial cells does not cause rupture of the capillary wall and capillary hemorrhage. An envelope of connective tissue, which is an essential part of the capillary wall, provides the resistance against rupture. The anatomic basis for capillary fragility or for any capillary hemorrhage is an injury of the connective tissue adventitia of the capillary.

AUTHOR'S SUMMARY

CHANGES IN THE KIDNEYS IN DIABETIC COMA AND DEATH FROM UREMIA AFTER TREATMENT WITH INSULIN E J KRAUS and H SELYF, Klin Wchnschr **7** 1627, 1928

Autopsy on three patients showed the kidneys to be swollen, yellow as with fatty changes and moist as though edematous. The histologic examination confirmed the general diagnosis of fatty changes in the kidneys of one patient, but in the other two patients, these were practically absent. There were hydropic changes and necrosis of the convoluted tubules. The anemia, especially that of the cortex, was especially noteworthy. The authors believe that after treatment with insulin the diabetic coma became a uremic coma, and that the kidney changes probably were an early stage of a glomerulonephritis.

E F HIRSCH

CONGENITAL DEFECTS OF THE RADIUS AND EAR AND FACIAL PARALYSES ERIK ESSEN-MOLLER, Ztschr f Konstitutionslehre **14** 52, 1928

In a girl, aged 6 weeks, the author records the occurrence of asymmetry of the face due to paralysis on the right side associated with furrowed, blunt tipped tongue, apical attachment of the frenulum, bilateral ranula, absence of the muscles

of the left ear, absence of the left auditory canal, and deformity of the left upper extremity consisting of kinking of the humerus, ankylosis of the elbow and terminal joint of the third left finger, complete absence of the radius and the phalanges of the first two fingers. The variations in facial expression due to the paralysis are portrayed. The left upper extremity is carried bent at the elbow with a radial deflection and pronation of the hand. A review of 200 instances in the literature is included. Some of the small bones of the wrist are absent in most instances. Defects of the ear were present in 20, facial paralysis was observed in 100. The latter condition is regarded as a disturbance of the peripheral neuron. The frequency of the occurrence of this condition in the Women's Clinic was 4 among 17,000 new-born infants. The condition may be bilateral. The etiology is somewhat indefinite, internal and external causes such as heredity, phylogenetic radial developmental defects, solitary and multiple genetic irregularities, as well as intra-uterine factors of pressure, faulty embryo enclosures and toxic substances were discussed. The author is inclined to disregard the external factors as causative and holds that, in his case and in most of those in the literature, the etiologic agency is concerned with one or more developmental arrestments in the embryo.

FRANK R. MENNE

THE SHRINKAGE OF PULMONARY TISSUE. F. KRAMPF, *Ztschr. f. Tuberk.* **51** 35, 1928

Shrinkage of pulmonary tissue is observed following pneumonia of varying etiology, after inhalation of dust, in tuberculosis and syphilis and in pulmonary abscess. All these processes are considered under the name of "primary inflammatory cirrhosis." Secondary inflammatory cirrhosis follows the inflammation of the bronchial system in so-called congenital bronchiectasis, in bronchial stenosis and in bronchial occlusion. Pulmonary cirrhosis may be produced artificially by the following procedures: ligation of branches of the pulmonary artery, more pronounced by the simultaneous ligation of the pulmonary veins, embolic occlusion of a branch of the pulmonary artery and simultaneous ligation of pulmonary veins. The consequences of pulmonary cirrhosis are as follows: local emphysema, secondary bronchiectasis and compensatory emphysema in the unaffected parts. Any cirrhosis concomitant with pleural adhesions causes shifting of the mediastinal structures, elevation of the diaphragm, deformity of the thorax and the vertebral column and peripheral stasis. The right side of the heart becomes hypertrophied and dilated, which, in its turn produces the well known clinical symptoms. Experimental work led to the following practical conclusions. The ligation of branches of the pulmonary artery is successful only in a limited number of cases of bronchiectasis. The simultaneous ligation of arterial and venous branches is impracticable on account of the frequent and severe nutritional disturbances. Ligation of pulmonary veins may be promising in some cases.

MAN PINNER

HEALING OF WOUNDS OF THE RENAL PELVIS AND URETER. Z. KAIRIS, *Ztschr. f. Urol.* **21** 615, 1927

Nephrotomy and pyelotomy are both used to remove stones from the renal pelvis. Each method has advocates who emphatically condemn any other. There has also been controversy over the way the wounds of the pelvis and ureter should be repaired after the stones are removed. Some operators use one type of suture, some another, and the operation in which a fibrous flap from the renal capsule or some of the perirenal fat is sewed over the wounds has proponents.

Kairis reports uneventful, spontaneous healing of such wounds, some quite large, purposely left unrepaired in fourteen patients with stones in either the ureter or the kidney pelvis, and in dogs similar wounds of the ureters healed, also without suturing, so that even microscopically there was scarcely any trace left.

E. R. LE COUNT



PERITONEAL PSEUDOMYOMAS ORIGINATING FROM VERMIFORM APPENDIX  
J NAESLUND, Upsala Lakaref Forh **34** 1, 1928

By tying the appendix off from the rest of the intestinal canal in new-born rabbits, Naeslund succeeded, within an observation period of 595 days, in producing well developed, large, distended formations filled with mucus (mucocèles), sometimes with diverticula. In a part of the cases, the mucocèles ruptured, the mucus in some instances reappearing later in pea-sized formations with epithelial cells, partly free, partly pedunculated, in the omentum. Small masses containing mucus and covered in places with epithelial cells were found also on the serous membrane of the small intestine. Pathologico-anatomic investigations were made in twelve cases of peritoneal-pseudomyomas which originated from the appendix in man and which were all found by accident, nine occurred in men, three in women, making a total published to date of forty-eight cases in men and forty-one in women. His results agree in the main with those previously published. The changes which he produced experimentally in rabbits coincided essentially with those found in peritoneal pseudomyomas in man. There are 136 illustrations and nine pages of bibliography.

CASE OF UTERINE ANGIOMYOMA E EHNMARK, Upsala Lakaref Forh **34** 219, 1928

Two uterine tumors were found in Ehnmark's case, the larger one a fibromyoma with red necrosis, the smaller one an angiomyoma. A full description is given.

DIFFUSE XANTHOMATOSIS OF SMALL INTESTINE H KEY, Upsala Lakaref Forh **34** 247, 1928

Key reports in detail a peculiar case with localization in the small intestine, discovered accidentally at necropsy in a woman, aged 67. He reviews the cases of xanthomatous changes in the stomach and intestinal canal published in the literature.

SUPRARENAL TUMORS N GELLERSTEDT and R HJELM, Upsala Lakaref Forh **34** 271, 1928

Roentgen examination in Gellerstedt and Hjelm's case, in a boy, aged 6, revealed a coral-shaped area of calcification above the left kidney. At necropsy, this was seen to belong to a tumor in the right suprarenal body, probably developed from the suprarenal cortex. The tumor consisted of a large number of sympathetic ganglion cells and nerve fibers, and was believed to be a ganglioneuroma. Because of the presence of many young and immature cells and the structure of the nervous tissue, it was classified as a ganglioblastoma.

MULTIPLE MYOMA OF COLON K G KLING, Upsala Lakaref Forh **34** 307, 1928

At the necropsy of a patient, aged 67 years, in whom a diagnosis of chronic colitis had been made, an extensive development of polypoid and sessile myomas, about the size of a hazelnut, was found in the lining of the entire large intestine. The tumors appeared to have developed from the muscularis mucosae.

CASE OF CIRCUMSCRIBED MYOSITIS OSSIFICANS IN BRACHIAL MUSCLE  
S ARNELL and R RUBEN, Upsala Lakaref Forh **34** 333, 1928

A round, hard tumor, without tenderness, proximal to the elbow fold, was noted in Arnell and Ruben's patient, one month after injury to the elbow. Roentgen examination revealed a calcified area, the size of a hen's egg, which was diagnosed as an ossified hematoma in the brachial muscle. Three months after the injury, the tumor began to decrease in size, and the bony structure became pronounced. Treatment consisted of massage and exercise during the first month after

the accident, after which the patient was able to work. In seven and a half months, the elbow function was completely restored and the osteoma was smaller. A month later, it was still further reduced in size and had the shape of a disk.

**PATHOGENESIS OF HYDROCEPHALUS** ARVID LINDAU, Arch path et microbiol Scandinav **5** 25, 1928

A summary is given of the formation, circulation and absorption of the cerebrospinal fluid (chiefly based on American investigations). On this basis, the nature and pathogenesis of hydrocephalus is discussed. Hydrocephalus is not a disease but a symptom of an occlusion in the circulating system of the cerebrospinal fluid. The author's method of injection of a dye at autopsy into the lateral ventricles to determine the site of the obstruction is described. This method may be employed as well in communicating as in noncommunicating hydrocephalus. Fifteen personally observed cases of hydrocephalus analyzed according to Dandy's principles are presented, among them is a case of external hydrocephalus.

AUTHOR'S SUMMARY

**HYPERPLASIA OF THE THYMUS WITH ENLARGEMENT OF THE PARATHYROIDS**  
H. BERGSTRAND, Acta path et microbiol Scandinav **5** 552, 1928

In a woman, aged 48, who died from cerebral hemorrhage, the thymus weighed 30.5 Gm and the parathyroids together weighed 1,370 mg. The enlargement of the parathyroids was due to newly formed parenchyma. The significance and relationship of these enlargements remain obscure.

**INTRA-ABDOMINAL HEMORRHAGE FROM RUPTURE OF CORPUS LUTEUM OF OVARIAN PREGNANCY** FRANCIS HARBITZ, Norsk Mag f Laegevidensk **89** 866, 1928

A case is described of hemorrhage into the abdominal cavity from rupture of a corpus luteum in which typical chorionic villi were found. The case illustrates that rupture of corpus luteum often is due to ovarian pregnancy, but in a previous study of fifteen or twenty instances, Harbitz did not detect any products of pregnancy.

## Pathologic Chemistry and Physics

**THE VOLUME OF THE BLOOD** D. C. DARROW and T. E. BUCKMAN, Am J Dis Child **36** 247, 1928

In infants with dehydration and in others with water retention, there is a tendency to reduction of the plasma volume. As the clinical picture improves in both types of cases, there is a return to the normal in the absolute plasma volume and the volume of plasma in cubic centimeters per kilogram of body weight. In subacute and chronic cases, the condition is one of oligemia rather than of anhydremia. In cases of dehydration, the loss of serum protein is generally proportionally less than the loss of plasma; in cases of retention of water, the loss of serum protein is generally proportionally greater than the loss of plasma volume. Thus the concentration of the serum protein is not a trustworthy index of dehydration or water retention, or of changes in blood volume. The concentration of the crystalloids is only slightly affected by the change in plasma volume.

H. E. LANDT

**THE INFLUENCE OF FEEDING ON CERTAIN ACIDS IN THE FECES OF INFANTS**  
J. R. GERSTLEY, CHI CHE WANG, R. E. BOYDEN and A. A. WOOD, Am J Dis Child **36** 289, 1928

The addition of an excess of lactose to breast milk causes little change in the excretion of the volatile acids, the titratable acid or the weight of the stools. The

addition of an excess of lactose to mixtures of modified cow's milk causes only slight change in the total excretion of the volatile acids, though it does decidedly increase the amount of free acid. The frequency and weight of the stools are also affected. The addition of 12 per cent lactose created a relationship of total titratable to total volatile acidity resembling that in breast milk. This may be due to the similar relations existing between lactose and protein in this formula. An excess of lactose in either breast milk or cow's milk did not result in an immediate disturbance of nutrition. An intercurrent bronchitis was a much more powerful factor in increasing the excretion of acid than any increase of carbohydrate in the mixtures. Following such a parenteral infection, the excretion of acid remained high for several weeks, although the infant remained clinically well. The addition of an excess of lactose at this time did not cause an immediate disturbance. These studies favor the Finkelstein hypothesis that intestinal fermentations are not primary but occur only after the development of some disturbance of nutrition.

AUTHORS' SUMMARY

COMPOSITION OF BONE. M. J. SHIAR and B. KRAMER, *J. Biol. Chem.* **79** 105, 121, 125 and 147, 1928

A technic is described for the analysis of minute amounts of pathologically calcified tissue. The methods presented have permitted the examination of such specimens as calcified, tuberculous lymph nodes, the calcified cusp of an aortic valve, etc. The Ca/P ratio was not found abnormal except in specimens of calcified fibroid of the uterus. The physicochemical mechanism of the calcification process is discussed.

ARTHUR LOCKE

ON THE TIME OF ABSORPTION AND EXCRETION OF BORIC ACID IN MAN. L. KAHLENBERG and N. BARWASSER, *J. Biol. Chem.* **79** 405, 1928

Boric acid passes through living skin with remarkable ease and rapidity. The carefully cleaned feet of three adult men were immersed in a saturated, aqueous solution of boric acid, held at 45°C. Samples of the urine were drawn from each subject at intervals of five and fifteen seconds and examined for the presence of borates. Traces were found, invariably, within from fifty to fifty-five seconds of the moment of immersion.

ARTHUR LOCKE

VITAMIN A DEFICIENCY AND CALCIFICATION OF THE EPITHELIUM OF THE KIDNEY. E. C. VAN LEERSUM, *J. Biol. Chem.* **79** 461, 1928

The calculi found in the bladders of rats maintained on a diet deficient in vitamin A probably develop from nuclei washed down from the tubules of the kidneys. The nuclei may be observed microscopically as crystalline concretions. The shape of these concretions, their possession of a kind of nucleus, their position against the membrana propria and their arrangement in a circle suggest that they may represent epithelial cells undergoing calcification.

ARTHUR LOCKE

ARTEFACTS AS A GUIDE TO THE CHEMISTRY OF THE CELLS. C. E. WALKER, *Proc. Roy. Soc. London* **103** B 397, 1928

The methods of fixation and staining which are used for the demonstration of "Golgi bodies" have been applied to emulsions of methyl myristate and laurate in mediums containing unsaturated lipids such as lecithin and cephalin. The descriptions of the final preparations appear to support the hypothesis that the Golgi elements are separations of cell lipid, produced during the drastic fixation processes necessary for their demonstration.

ARTHUR LOCKE

## Microbiology and Parasitology

CLOSTRIDIUM WELCHII SEPTICEMIA COMPLICATING PROLONGED LABOR DUE TO OBSTRUCTING MYOMA OF UTERUS P TOOMBS and I MICHELSON, Am J Obst & Gynec **15** 397, 1928

In addition to a detailed report of their own case, the authors collected from the literature the reports of forty-one cases of puerperal sepsis due to *Clostridium welchii*. There are two main groups, the abortion group comprising 60.97 per cent, and the nonabortion group, 39.03 per cent, of the total cases. The latter group was divided into subgroups which can include any possible condition that delays the progress of the child through the birth canal. The introduction of the organism is favored by too frequent vaginal examinations. Criminal abortions or operative procedures favor the implantation of the organism in the first group.

A J KOBAK

SEX DIFFERENCES IN THE PATHOLOGIC PICTURE OF SYPHILIS A SCOTT WARTHIN, Am J Obst & Gynec **15** 595, 1928

Latent syphilis is a common form of the disease in the female. If the spirochete enters through the cervical or uterine columnar cell mucosa, the primary lesion may be absent or may escape detection entirely, being smaller and less indurated than in the male, and the diagnosis may be missed. When present on stratified epithelium of the cervix, clitoris, urinary meatus or nipple, it is frequently mistaken for carcinoma. The skin lesions of the secondary stage are milder, or may be entirely absent, but there is a greater preponderance of constitutional symptoms, particularly arthritic manifestations, during this stage. In the majority of women, late syphilis is latent during the child-bearing period, accompanied by apparent good health and a negative Wassermann reaction, nevertheless, these patients may bring forth syphilitic children with involvement of all the fetal adnexa. The central nervous system, heart and aorta less frequently are involved, and the ovary is practically immune to the lesion. On the contrary, the liver, pancreas, suprarenals and rectum are more prone to spirochetal invasion. There is, therefore, a relatively greater immunity in the female, and the general aspects of the disease appear milder. At the menopause, signs of syphilis and a positive Wassermann reaction may be present. While there is a general modification of the disease as a whole, in the female, there is, in addition, a marked resistance of certain organs to the spirochete.

A J KOBAK

SUBACUTE BACTERIAL ENDOCARDITIS OF STREPTOCOCCUS VIRIDANS TYPE IN PREGNANCY, WITH TWO CASE REPORTS H G WALSER, Am J Gynec & Obst **15** 840, 1928

Two cases of typical subacute bacterial endocarditis are reported, the blood cultures taken during pregnancy revealed *Streptococcus viridans*. The clinical manifestations were of the usual type. In one case, after a full term delivery, the blood from the umbilical cord was positive for *Streptococcus viridans*, although the child did not show subsequent clinical disturbance, and the placenta was apparently normal. In the other case, blood cultures obtained from the mother during pregnancy showed *Streptococcus viridans*, and throat culture a predominating nonhemolytic streptococcus. The infant died seventeen hours after premature birth, with definite signs of intra-uterine infection, transmitted apparently through the placenta. Postmortem examination of cultures from the heart blood showed a nonhemolytic streptococcus, in addition, there were multiple infarctions of the brain. Postmortem examination of the mother was not made. Thus Walser showed that the fetus can be infected in maternal infection. The course of the disease or pregnancy was not particularly affected.

A J KOBAK

THE PATHOLOGY OF YELLOW FEVER IN MAN AND MONKEY N PAUL HUDSON,  
Am J Path 4 395, 407 and 419, 1928

The lesions in *Macacus rhesus*, brought about by experimental infection with yellow fever virus, seem to result from a severe intoxication, as in the case of yellow fever in man, recently expressed by Klotz and Simpson. Neither in the monkey nor in man is there any evidence of the localization of the virus. We have been unable to find any constant bacterial form, or leptospiras or spirochetes demonstrable in Levaditi preparations either in cases in human beings or in experimental tissues. The specimens of the liver from the monkey tend to confirm the fact that necrosis in the liver is essentially midzonal in type in yellow fever, with less altered cells increasing toward the periphery of the region involved. Likewise, as in cases in man, when the degenerative changes approach the limiting structures of the lobule, the most extreme necrosis is usually in the midzone. Klotz and Simpson have recorded that in the spleen there is a sequence of changes involving the lymph follicles, from early enlargement of the follicle due to hyperplasia of the endothelial elements, followed by loss of lymphocytes, to final degeneration of the endothelial cells. We have not observed the first stage given in tissues from man or from monkey, otherwise, a study of the rhesus sections makes it evident that the process described by these workers is probably correct. A stage of necrosis is obvious in the monkeys, but is uncommonly seen in the spleens of human beings, in which it is possible the stage might have been passed at the time of death. We would add, however, that in monkeys, degeneration and necrosis involves the lymphoid as well as the endothelial elements of the follicles. The fatty degeneration of the fibers of the heart muscle and the same and other acute degenerative changes of the kidney in the rhesus monkey add to the evidence for the clinical manifestations of this disease in man. If experience bears out the hope that *M. rhesus* is regularly susceptible to the yellow fever virus, this animal will prove to be of incalculable value in the diagnosis of yellow fever in man because of the remarkably accurate reproduction of gross and microscopic lesions.

AUTHOR'S SUMMARY

MYOCARDIAL DEGENERATIONS IN YELLOW FEVER D E CANNELL, Am J Path 4 431, 1928

Cloudy swelling and granular and fatty degeneration were found constantly in the hearts of both the cases in man and those experimentally induced in *Macacus rhesus*. Primary inflammatory changes were not seen in the heart in yellow fever. Secondary response of the white blood cells to intense degeneration was observed in two cases in human beings. The distribution and intensity of granular and fatty degeneration were patchy and variable both in cases in man and those in *Macacus rhesus*. Fatty degeneration was most marked in the neighborhood of the nuclei of the fibers. The causation of the slow pulse in yellow fever is still uncertain, and doubt is thrown on the belief that it is due to the jaundice. Further investigation of the clinical function and the pathologic changes in the bundle of His may lead to the solution of the problem. The lesions in the hearts of human beings and in those of *Macacus rhesus* are essentially the same. The lesions in the heart are in themselves not sufficient to make a diagnosis of yellow fever.

AUTHOR'S SUMMARY

DISSOCIATION OF THE RAWLINGS STRAINS OF B TYPHOSUS NEWTON W LARKUM, Am J Pub Health 18 647, 1928

As a result of reports that growth of R types in homologous immune serum resulted in reversion to S types, studies of the nature of the Rawlings strains of *B. typhosus* were carried out in order to determine the state of the culture and the extent to which dissociation might be controlled. It has been generally accepted that the R type was avirulent or less virulent than the corresponding S type. Hence, if the strains of *B. typhosus* used in vaccines to produce immunity should

be of the R type, the antiserum resulting would tend to convert the less virulent organisms entering the individual, if infection occurred with such types, into more virulent forms and, furthermore, would tend to prevent the usual dissociation in case of infection with a virulent organism. The desirability of using only S type cultures to produce immunizing vaccines is thus emphasized.

A study of six strains of *B. typhosus*, Rawlings, actually in use in as many laboratories in the United States, reveals that in only one case is an S strain in use. It is recommended that—since animal passage can usually change an R to an S type—laboratories making vaccines follow this procedure.

BACTERIUM ABORTUS INFECTION IN MAN JAMES G MCALPINE and FRIEND  
LEE MICKLE, Am J Pub Health 18 609, 1928

Ten thousand, one hundred and fifty-seven samples of serums from human beings, which were submitted for the Wassermann examination, were tested by the agglutination reaction, *Bacterium abortus* being used as the antigen. Of this number, approximately 0.6 per cent gave reactions up through the 1-100 dilution. These results, which were obtained in a state in which preliminary testing has shown at least 90 per cent of the dairy herds to be infected with *B. abortus* and approximately only 60 per cent of the milk to be pasteurized, indicate that the infection of man with the bovine type of *B. abortus* is relatively rare, provided any significance can be attached to the agglutination test. Attempts to follow the small number of cases reacting through the 1-100 dilution by the agglutination test were made through questionnaires, subsequent testing and blood cultures. This method was unsatisfactory on the whole, as many of the patients remained under the care of the attending physicians for only a short time.

AUTHORS' SUMMARY

TORULA INFECTION IN MAN O BERGHAUSEN, Ann Int Med 1 235, 1927

The literature affords twenty-four examples of torula infection in man, to which Berghausen adds a case. *Torula histolytica* is a member of the group of blastomycetes known as *Fungi imperfecti*, *Oidium*, *Monilia* and *Dematium* comprise the other members of the group. In Berghausen's case, *Torula histolytica* was isolated from a large ulcer of the tongue. The patient died. There was some clinical evidence of involvement of the lungs, but postmortem confirmation could not be made, since autopsy was refused.

WALTER M SIMPSON

CHRONIC ULCERATIVE COLITIS H W SOPER, Ann Int Med 1 313, 1927

Soper isolated the Bargen-Logan diplococcus in all of sixteen cases of chronic ulcerative colitis in which a search for the organism was made. The conclusion is reached that the Bargen-Logan diplococcus is the primary etiologic agent in this disease.

WALTER M SIMPSON

THE HISTOPATHOLOGY OF THE TONSIL IN ACUTE RHEUMATIC FEVER AND CHOREA W W G MACLACHLAN and DEW G RICHEY, Ann Int Med 1 506, 1928

MacLachlan and Richey attach importance to the perivascular lymphoid and plasma cell lesions found in the capsule and pericapsular tissues of the faucial tonsil in fourteen of eighteen cases of rheumatic fever and in four of five cases of chorea. Endothelial proliferation of the lining cells of the capillaries and perivascular lymph spaces was observed in eleven instances, and in six cases the endothelial cells were multinucleate and associated with granulomatoid lesions, suggesting the so-called Aschoff nodules. The writers hesitate to state that such lesions in the tonsil are specific for rheumatic fever or chorea.

WALTER M SIMPSON

SOME CONSIDERATIONS UPON THE ETIOLOGIC AGENT IN YELLOW FEVER  
ARISTIDES AGRAMONTE, Ann Int Med 1 977, 1928

Agramonte concludes that the etiologic agent of yellow fever has not been demonstrated. The claims of Noguchi and other investigators that *Leptospira icteroides* is the specific germ of yellow fever have been conclusively disproved because (a) *L. icteroides* and *L. icterohemorrhagiae* show crossed serologic reactions indicating their identity (b) Serum from patients convalescing from yellow fever does not protect against *L. icteroides*, while serum from patients convalescing from Weil's disease does protect against both *L. icteroides* and *L. icterohemorrhagiae* (c) *L. icteroides* gradually increases in numbers in the blood of inoculated animals, while the real yellow fever germ disappears from the circulating blood at the third or fourth day (d) *L. icteroides* fails to infect mosquitoes so that in due time they may infect man (e) *L. icteroides* can penetrate the unbroken skin and produce infection, while yellow fever has been shown to be noncontagious, even through cuts or abrasions of the skin. Any vaccine or serum prepared with the *L. icteroides* cannot be of value, either protective or curative, as regards yellow fever.

WALTER M. SIMPSON

METADYSENTERY A. CASTELLANI, Ann Int Med 2 155, 1928

Organisms of the metadysentery group have been found in many clinical conditions, with either simple diarrhea or dysenteric diarrhea. The paper directs particular attention to a chronic type of colitis characterized by recurrent attacks of diarrhea, generally simple, but occasionally dysenteric. The metadysentery bacilli are intestinal organisms similar to the dysentery bacilli, Shiga and Flexner, in that they do not produce gas in any sugar. They differ, however, in that they clot milk or produce acidity in lactose, they clot milk without producing distinct acidity in lactose, or they produce acidity in lactose without clotting milk. Some species (*Lankoides-Dysenteroides* group) are pathogenic, while others probably are not. *Bacillus metadysentericus* is pathogenic. In the chronic conditions, the blood generally contains a large number of agglutinins for the variety of metadysentery bacillus isolated from the patient's stools.

WALTER M. SIMPSON

SECOND INFECTION IN SYPHILIS C. R. L. HALLIDAY and H. WASSERMAN, Arch Int Med 41 843, 1928

A statistical study has been made of case reports in the literature since 1910 of second infection with syphilis, and to this number there are added eight new cases from the Johns Hopkins Hospital Clinic. The total number of cases accepted is 237, while 447 were rejected as not fulfilling the condition adapted for this study. Two hundred and thirty-two of these patients, or 97.8 per cent, were treated for the first infection during the primary or secondary stage. The duration of infection before the first treatment is known in eighty-three cases. Practically all of these were first treated before the end of sixteen weeks, and sixty-eight before the end of eight weeks. Second infection occurred in four patients, or 1.6 per cent, who had syphilis in a latent or late form at the time they were first treated for the disease. Second infection occurred in one patient, or 0.4 per cent, who presented undoubted evidence of congenital syphilis. The expressed relation of the time of treatment of the first infection in man and the incidence of second infection is paralleled closely by data collected on 328 rabbits experimentally injected with syphilis. It is indicated that the duration of a first infection before treatment has an important bearing on the patient's acquired resistance to a second infection.

H. R. FISHBACK

MICROBIC DISSOCIATION IN STREPTOCOCCI L. O. DUTTON, J. Bact 16 1, 1928

As a basis for future work some of the more common variations of the colonies in streptococcal colonies have been described. Little is clear concerning the sequence

of the types of colonies, but it is apparent that most of the variations of the colonies that have been described for other bacterial species occur also in this group. The S type colony is clearcut, while the R type is not so definite. There are many intermediate types. In fluid mediums agglutination is associated with the R types. Certain variations also parallel the types of colonies, diplococcic and gram-positive, regular cells being of the S type, while long-chained, irregular, gram-variable forms are of the R type. In natural infections, virulence seems also to parallel the types, the S type being virulent, and the R types being relatively avirulent.

## AUTHOR'S SUMMARY

PHYSICAL AND BIOLOGICAL CHARACTERISTICS OF LEPTOSPIRA I. J. KLIGLER and M. ASHNER, J. Bact. **16** 79, 1928

Morphologically, *Leptospiras* are exceedingly variable, the form and size depending on the medium, temperature and rate of growth. These organisms carry a positive charge at ordinary reactions, but at  $p_H$  9.2 they become negatively charged. The important distinguishing characters which differentiate *Leptospira* from some of the true viruses are sedimentability and filtrability. *Leptospira* may be sedimented by prolonged centrifugation at 3,000 revolutions. From four to five hours seem to suffice practically to free a suspension of these organisms. Although they pass readily through a Berkefeld or Seitz filter, only a relatively small proportion of the organisms pass through. *Leptospiras* are readily cultivable on artificial mediums. The most satisfactory procedure for primary cultivation from infected animals is to cover the blood-free fibrin clot, or the sedimented red cells, with a small amount of Noguchi's leptospira medium (to a height of from 1.5 to 2 cm). *Leptospiras* are obligatory aerobes and the pathogenic forms die promptly when placed under anaerobic conditions.

## AUTHORS' SUMMARY

THE ACTION OF IRON AND CITRATE IN SYNTHETIC MEDIA FOR TUBERCLE BACILLI GUILFORD B. REED and CHRISTINE E. RICE, J. Bact. **16** 97, 1928

Data have been presented to show that the addition of iron in the form of chloride or sulphate to a synthetic medium, consisting of asparagin, glycerol, disodium acid phosphate and sodium chloride over the ordinary  $p_H$  growth range of tubercle bacilli, results in almost, though not quite, complete precipitation of the iron. The addition of sodium citrate, probably through the formation of complex ions, inhibits the precipitation of iron over this  $p_H$  range. In a synthetic medium adjusted to  $p_H$  7.4, it has been shown that tubercle bacilli produce approximately 20 per cent more growth when iron and no citrate is added, and slightly over 100 per cent more growth when both iron and citrate are added to the medium. In more acid and more alkaline mediums less conspicuous advantages result from the addition of iron. Similar results are obtained with the growth of *B. phlei* and *B. lepro* in these mediums.

## AUTHORS' SUMMARY

VARIATIONS OF STREPTOCOCCI WITH A NOTE ON HEMOLYSIN PRODUCTION M. FROBISHER, JR., and E. R. DENNY, J. Bact. **16** 109, 1928

For the study and proper classification of streptococci in blood agar the following are essential. The differentiation of types based on low power microscopic observation of deep and not of surface colonies in blood agar plates. The use of tube hemolysin tests with properly prepared cultures to supplement plate observations. Genuine, alpha type streptococci have frequently been encountered which possess marked hemolytic powers, producing hemolytic zones from 2 to 4 mm wide and appearing, to the naked eye, to be beta type (hemolyticus) streptococci. These strains never caused hemolysis when their broth cultures were mixed with red cell suspensions. When the deep colonies of such streptococci in blood agar pour plates were viewed with the low power microscope, they were seen to have about them, inside the hemolytic zone, the zone of methemoglobinized cells common to all alpha type streptococci. A number of such streptococci have been found to



lose a large part (not all) of their hemolytic powers after being kept for some time under various artificial conditions, and to appear like the ordinary and easily recognized alpha type of streptococcus. The diminution of hemolytic properties may be due to a change in the organisms or to some obscure variation in technic. It is suggested that some of the reported mutations in which a beta type streptococcus has been said to change into an alpha type streptococcus may be due to failure to recognize the true character of the organism in the first place, accompanied by a diminution of the original hemolytic properties. It is possible that many of the anomalous results of many sorts reported by investigators of streptococci may be due to confusion in the identification of the alpha and beta types.

## AUTHORS' SUMMARY

STREPTOCOCCUS VIRIDANS DERIVED FROM SINGLE CELL STRAINS OF STREPTOCOCCUS HEMOLYTICUS. FRANCIS B. GRINNELL, J. Bact. **16** 117, 1928

Single cell strains of hemolytic streptococci may under certain conditions of cultivation give rise to daughter strains of the alpha type. These alpha variants resemble *Streptococcus viridans* in every respect. The change from the beta to the alpha type occurs only with certain strains. The change is characterized by the occasional appearance of alpha type colonies, and there is not as a rule a complete change of the whole culture to the alpha type similar to the change from S to R with pneumococci. The alpha variants remain true to type with no tendency to revert under the usual conditions of cultivation. The loss of hemolytic power is accompanied by a slight loss of virulence. The alpha derivatives usually but not always give the same fermentation reactions as the beta strains from which they are derived.

## AUTHOR'S SUMMARY

HEMOLYSIS BY PATHOGENIC BOVINE STRAIN OF *B. COLI*. MARION L. ORCUTT, J. Bact. **16** 123 and 135, 1928

Studies on the hemolytic properties of one strain of *B. coli* isolated from a bovine source showed that the hemolytic power parallels the number of living organisms present in culture, but that this is not the case in the presence of inhibiting factors. Veal infusion broth inhibited hemolysis without inhibiting growth, but this power became less marked when the broth was filtered or diluted. In certain concentrations peptone alone had an inhibitory effect on hemolysis.

In the second report, inhibition of hemolysis was demonstrated in normal serums from the horse and cow, and from man. Cholesterol alone produced some inhibition of hemolysis but the concentration of this agent did not parallel the degree of inhibition. Specific immune serum prevents hemolysis more than normal serum. The author concludes that the inhibiting power of any given serum on hemolysis may be due to a combination of factors including cholesterol, protein composition and specific antibody content, but that the different inhibiting values of different normal serums seem to be related chiefly to their protein composition.

## EDWIN P. JORDAN

A COMPARATIVE STUDY OF THE ACTION OF SODIUM RICINOLEATE ON BACTERIA. ANTHONY KOZIOWSKI, J. Bact. **16** 203, 1928

Among the streptococci investigated, those isolated from cases of erysipelas, measles and scarlet fever were the most susceptible to the bactericidal action of sodium ricinoleate. They were killed by this soap in a dilution of 1:5,000 in about seven hours or sooner at 35 C., in a control culture, without soap, they survived for more than one week, their growth was inhibited by this soap in a dilution of 1:20,000 or less, in their cellular susceptibility they approach that of pneumococci which were killed by the same soap, under similar conditions, in a dilution of 1:10,000. Pneumococci are dissolved quite readily by sodium ricinoleate in a dilution of 1:5,000, in this regard they differ from other bacteria investigated. Of the bacilli, *B. diphtheriae* was found to be quite susceptible to

the inhibitory, and much less to the bactericidal, action of sodium ricinoleate, *B. tuberculosis* showed a slight susceptibility, as it was inhibited in its growth by this soap in a dilution of 1:2,000, *B. paratyphosus*, *B. dysenteriae*, *B. coli communis* and *S. fecalis* are fairly resistant to the inhibitory and bactericidal action of sodium ricinoleate. They are probably adapted to the action of soaps in their natural conditions of growth. An intermediate place between susceptible and nonsusceptible bacteria is taken by some streptococci which are more or less saprophytic, i. e., *S. lacticus*, *S. pyogenes* and *S. viridans*. These were inhibited in their growth by sodium ricinoleate in a dilution of 1:5,000 or lower, but were not killed in a dilution of 1:1,000. The bactericidal effect of sodium ricinoleate is conditioned by the specific cellular susceptibility of the bacteria, and further by the concentration of the soap solution, by the time and the temperature of exposure. The difference in the cellular susceptibility of various strains of the groups of streptococci, isolated from cases of measles, scarlet fever and other infections, might be helpful in bacteriologic investigations. Sodium ricinoleate may be used instead of bile for the dissolution of pneumococci in diagnostic routine work.

## AUTHOR'S SUMMARY

BACTERICIDAL PROPERTIES OF THE ACYL AND ALKYL DERIVATIVES OF RESORCINOL  
BETTY LEE HAMPHILL, J. Infect. Dis. **43**: 25, 1928

From a detailed study of the alkyl and acyl derivatives of resorcinol and some of the intermediate ketones, the following are some of the chief results. An elevation of temperature from 20 to 37°C increases the bactericidal action of all derivatives tested, in the presence of organic material at 37°C both series tend to lose their bactericidal activity, in alkaline solution the alkyl resorcinols are increased in bactericidal activity beyond the hexyl compound, and the disinfecting power of these derivatives in general depends mostly on their solubility in water.

## AUTHOR'S SUMMARY

INFLUENCE OF CARBOHYDRATES ON BACTERIAL DECOMPOSITION OF UREA  
MITSUTERU ISHIKAWA, J. Infect. Dis. **43**: 67, 1928

*B. ammoniagenes*, *B. aerogenes*, *B. morganii*, *B. proteus vulgaris* and *Staphylococcus aureus* actively decompose urea in culture mediums, the washed cells of these bacteria also possess a definite urea-splitting activity.

The presence of an utilisable carbohydrate accelerates the disintegration of urea by these bacteria, cultured and washed. Sodium formate added to the culture medium does not exert any increasing effect.

Thymol has an inhibitory influence on the liberation of ammonia from urea, by cultured or washed organisms, in the presence or absence of dextrose.

The symbiosis of an urea-splitting organism with a nonurea-decomposing bacterium, in a medium containing a carbohydrate fermentable by the latter organism but not by the former, increases the generation of ammonia, in comparison with the single culture of the urea-splitting organism.

## AUTHOR'S SUMMARY

BEHAVIOR OF BRUCELLA ORGANISMS TOWARD GENTIAN VIOLET  
I. FOREST HUDDLESON and ELIZABETH ATELL, J. Infect. Dis. **43**: 81, 1928

Varieties, and strains within a variety, of the genus *Brucella* exhibit a difference in sensitiveness to gentian violet in a medium, expressed in degree of growth. The growth of strains of the variety of *B. melitensis* and *paramelitensis* is not inhibited on a medium by the presence of gentian violet in dilutions of 1:100,000 and 1:250,000. A few of the strains are slightly inhibited by the presence of a 1:50,000 dilution of the dye. Strains of the variety of *B. abortus* may be divided into two groups as regards their ability to grow on a medium in which gentian violet is present, namely, those which are markedly inhibited and those which fail to grow in the presence of 1:50,000 and 1:100,000 dilution of the dye. The

latter group contains one bovine strain, several human strains and all porcine strains in the possession of the writers. The difference in dye sensitivity may prove to be a means of distinguishing strains of the abortus variety not otherwise distinguishable

## AUTHORS' SUMMARY

# THE ACTION OF PHENOL AND FORMOL ON AEROBIC AND ANAEROBIC ORGANISMS JOSEPH P. SCOTT, J Infect Dis 43 90, 1928

It is shown that phenol in strengths up to 5 per cent acts slowly on anaerobic organisms, while formaldehyde in dilutions of from 0.5 to 0.75 sterilizes anaerobic cultures rapidly,

The greater susceptibility of aerobic spore-forming organisms to these disinfectants make it possible to eliminate aerobic contaminations from anaerobic cultures by the use of 0.5 per cent phenol or formol

## AUTHOR'S SUMMARY

# RICKETTSIA OF ROCKY MOUNTAIN SPOTTED FEVER IN THE BRAIN OF THE INFECTED GUINEA-PIG HOBART A. REIMANN, J Infect Dis 43 93, 1928

In the examination of guinea-pigs infected with Rocky Mountain spotted fever, *Rickettsia* were found in only one of eight brains, which was within a vein of the cerebrum and not in the brain substance. If the blood of the brain is responsible for the infectiousness of this tissue the question arises concerning the arbitrary infectious dose of the brain of animals killed by exsanguination. Because *Rickettsia* are small and are easily decolorized in the course of staining it is possible that they have been overlooked

## AUTHOR'S SUMMARY

# SURFACE TENSION IN RELATION TO BACTERIAL GROWTH WITH SPECIAL REFERENCE TO LACTOBACILLUS ALEXANDER ALFRED DAY and WILLIAM MERRIOTT GIBBS, J Infect Dis 43 97, 1928

The effect of lowered surface tension on the development of *L. acidophilus* and *L. bulgaricus* was studied. The surface tension was depressed by applications of four soaps, together with sodium ricinoleate, sodium oleate and sodium taurocholate

No instance was found in which inhibition of growth could be attributed to lowered surface tension

Sodium ricinoleate exerted a toxic action toward both *L. acidophilus* and *L. bulgaricus*, but this action could not be used as a means of identifying the two organisms

The fermentation of maltose, sucrose and levulose does not offer a means of differentiating *L. acidophilus* from *L. bulgaricus*

## AUTHORS' SUMMARY

# MONILIA FROM OSTEOMYELITIS CHARLES L. CONNOR, J Infect Dis 43 108, 1928

A budding yeast-like organism forming reluctantly a mycelium in certain culture mediums and otherwise behaving as *Monilia* was isolated from an abscess of the buttock which communicated with the iliac bone. There had been a long-standing osteomyelitis of the humerus, and the organisms were seen in tissues from this lesion also. This strain of *Monilia* corresponds with no described species so far as fermentation tests are concerned, but it is pointed out that such tests are unreliable as a means of differentiating the group of organisms variously called *Torula*, *Cryptococcus*, *Blastomyces*, *Oidia*, *Monilia* or *Oospora*. A review of the characters by which these organisms are classified shows that they do not differ sufficiently to be given different names, that, in fact, they represent only two different types, namely, a mycelia-forming group (*Blastomyces*, *Oidia*, *Monilia*, *Oospora*, all classified as *Parasaccharomyces* by Anderson), and a

nonmycelia-forming group (*Toxula* or *Cryptococcus*) These two groups with a third, *Mycoderma*, provide for all those yeast-like organisms known as *Fungi imperfecti* The nature of these organisms does not permit at present of a more elaborate classification

## AUTHOR'S SUMMARY

BACTERIAL ADAPTATION TO ACRIFLAVINE VICTOR BURKE, CATHERINE ULRICH and DON HENDRIE, J Infect Dis **43** 126, 1928

*Staphylococcus albus* shows increased tolerance for the antiseptic dyes after from six to eight hours' exposure This adaptation to the dyes is temporary and disappears when the organism is grown on dye-free agar Delayed growth of the organism in the presence of the dye is due in part at least to the process of adaptation of the organism to the dye The increased tolerance of the organism for the dye is partially specific *Staphylococcus albus* can be separated into two strains which differ in their ability to tolerate neutral acriflavine

## AUTHORS' SUMMARY

CHOICE OF ANTISEPTIC DYE IN MIXED INFECTIONS VICTOR BURKE, M P JESSUP and SMITH PHILIPS, J Infect Dis **43** 131, 1928

Gentian violet is more bactericidal than neutral acriflavine for both the gram-positive and the gram-negative organisms commonly found in wounds Blood reduces the bactericidal action of both dyes No advantage is gained by mixing the two dyes The dye most effective against the most resistant organism in the wound should be used

Since bacteria acquire specific dye tolerance in a few hours rotation of dyes in the treatment of infections may be beneficial

The bactericidal strength of neutral acriflavine varies with the manufacturer Different samples from the same manufacturer are nearly uniform in bactericidal action

## AUTHORS' SUMMARY

TRACHOMA STUDIES IDA A BENGTON, Pub Health Rep **43** 2210, 1928

The microscopic evidence in a study of film preparations and sections of conjunctivae and tarsi from cases of trachoma is that the inclusion bodies in the epithelial cells originate from rod-shaped micro-organisms which tend to occur as diplobacilli, and that the development of the inclusion body after the entrance of the rod into the cytoplasm of the cell is due to the multiplication of the organism and subsequent reaction on the part of the cell against the invading bacteria, transforming them into the small reddish-staining coccoid forms designated by von Prowazek as "elementary bodies" with the blue-staining "mantle" which represents the partially dissolved portion of the bacteria The "free Lindner initial bodies" appear to be pleomorphic or modified forms of rod-shaped bacteria which have been seen rather infrequently outside the cells and which occur as blue-stained oval or cylindrical bodies stained at the rim and bipolarly These are probably also formed as the result of the action of conjunctival fluids on the rod-shaped micro-organisms In interpreting the inclusion body, the "elementary bodies" and the "free initial bodies," the fact must be borne in mind that they are found in the conjunctiva which, on account of its exposure, is particularly liable to the invasion of micro-organisms and must, therefore, be unusually rich in protective substances which are probably lytic in action These act on the bacteria to destroy or inhibit their growth, and it is not surprising that the latter should be changed into forms which are quite unrecognizable when compared with those occurring in artificial culture mediums containing none of these substances antagonistic to their growth

It has been possible to produce experimentally forms corresponding in appearance to the so-called "elementary bodies" of von Prowazek and the "initial bodies"

of Lindner, by the inoculation of certain gram-negative rod-shaped organisms isolated from the conjunctiva of trachoma cases, into the conjunctiva of guinea-pigs. A study of preparations made a short time after the inoculations suggests that the "elementary bodies" and "initial bodies" represent modifications of the organisms originally introduced which are brought about by the action of lytic substances contained in the conjunctival fluids and tissues.

The results of the work considered do not prove or disprove that the "elementary bodies," "initial bodies" and inclusion bodies are concerned etiologically in trachoma. This discussion is presented merely to show that these bodies in all probability are bacterial in character, and that the bacteria from which they originated are rod-shaped in form. The fact of their presence in a considerable percentage of cases of trachoma is an indication that they may be of etiologic significance, but the question cannot be answered definitely as yet.

#### AUTHOR'S SUMMARY

RAT BITE FEVER. E. N. McDIRMOTT, *Quart. J. Med.* **83** 433, 1928

In 1926, a case of rat bite fever was discovered in Edinburgh, and a strain of *Spiracheta morsus-muris* was isolated and its effects on animals investigated. One of the results was the analogy observed between the disease in certain animals and in syphilitic infection in man. Chill and fever may develop about thirty days after the bite has been received, but Japanese authors have claimed that the incubation period may be as long as two years. The wound heals rapidly, later pain is felt in the scar, and the surrounding area becomes swollen. Vesicles develop and ulceration ensues, the surface of which gives off a serous discharge, in which the organism is frequently demonstrable. Regional lymphadenitis follows. The temperature returns to normal, but an intermittent fever soon sets in. Malaise occurs with the attacks of fever, which is also accompanied generally by a maculopapillary eruption, which may be widespread. In long standing cases, a moderate degree of anemia develops. Occasionally, there are pleurisy and bronchitis, and in long-continued cases constipation is usual. The spleen is generally not involved. In the kidneys there is usually no involvement, except in severe cases, in which a toxic nephritis is common. Pains of the joints and periosteitis occur. The Wassermann reaction is positive in about 50 per cent of cases, and about 10 per cent of patients not treated die, but the mortality is negligible in the patients treated with neoarsphenamine. The postmortem observations may be summarized as follows: generalized marasmus, parenchymatous degeneration of the heart, liver and kidneys, catarrhal gastro-enteritis, catarrhal cystitis, meningeal hyperemia and edema, hyperplasia of the lymph glands, hyperemia of the suprarenal cortex, spleen and kidneys, and hyaline degeneration of the central arteries of the malpighian bodies in the spleen. In 1916, the causal spirillum was isolated by Japanese workers. Streptococci and bacilli were found in other cases, but these may be considered as secondary invaders. The strain studied by the author was isolated from a boy who was bitten on the forehead. About two weeks after this he was unwell, and a swelling developed, a few days later the regional lymph glands were enlarged. About a month after he received the bite he was feverish, and the brow and forehead were markedly swollen. He developed four attacks of high fever in the hospital, and a number of the cervical glands were excised on the forty-ninth day. The condition cleared up under treatment with neoarsphenamine. Emulsions of the glands were injected into two guinea-pigs, and spirilla appeared in their blood after nineteen and thirty-seven days. The organism is rapidly moving, refractile and stains deep violet with the Romanovsky stain, it is gram-negative, may be blunt or pointed, and may measure from 1.5 to 10 microns, with numerous flagella, it divides by transverse fissure and is extremely difficult to grow in laboratory mediums. Mice, rats, guinea-pigs, rabbits, cats and ferrets were injected, all of which developed lesions.

THE BACTERIOLOGY OF SPRUE F P MACKIE, S N GORE and J H WADIA,  
Indian J M Research **16** 95, 1928

The blood culture during life from thirty patients with sprue yielded an unknown bacillus in two. The rest were sterile to both bacteria and yeast. Protozoa such as amebas and flagellates are excessively rare in the feces in cases of sprue—probably as a result of their high acidity. Ninety-two specimens of feces from patients with sprue have been closely studied and a complete analysis of the last series of fifty-one cases is given in this paper. Not once in this series was a recognized pathogen isolated, though an atypical strain resembling *B dysenteriae* (Flexner) was found once. *B dysenteriae* (Strong) once, and organisms like *B morgan*, *carolinus*, *columbiensis*, *asiaticus*, which are of doubtful pathogenicity, were each isolated on a few occasions. Hemolytic gas-producing anaerobes were not examined for in all cases but were invariably present when suitable cultures were made. As these organisms are almost invariably present in normal stools, the mere fact of their presence in stools in cases of sprue cannot in itself be claimed as significant. The duodenal contents of eight cases received particular attention. None was sterile. One case yielded five types of bacteria, one case, four, three cases, three, and two cases, two. A hemolytic streptothrix was present in two cases. Hemolytic strains of *B coli* were not isolated, nor were anaerobes of types of *B welchii* found in any of the eight samples. Half the strains of cocci were hemolytic, and a number of strains of hemolytic gram-positive aerobic bacilli were isolated from the duodenal contents. We may conclude that the duodenal contents from patients with sprue are rich in bacteria and that a number of these are powerful hemolytics. None of these could be definitely identified with the recognized pathogenic bacteria which are found in the intestinal canal in other diseases.

AUTHORS' SUMMARY

COMPARATIVE INOCULATIONS OF BR ABORTUS AND BR MELITENSIS IN THE  
GOAT E BURNET, Arch Inst Pasteur de Tunis **17** 108, 1928

The goat is susceptible to both the organisms which cause abortion in this animal. The susceptibility is somewhat more marked with respect to *Brucella melitensis*. It has been supposed that *B abortus* may become virulent for man on passage through the goat, and the fact that undulant fever in man is acquired easily from the goat would support this idea. It is not possible to trace definitely the evolution of *B abortus*, but it will be necessary in the further study of the epidemiology and prophylaxis of undulant fever to compare the pathogenic power of *B abortus* for different species of animals.

THE ALBUMIN-GLOBULIN RATIO IN THE SERUM, SEDIMENTATION SPEED OF  
ERYTHROCYTES AND PIRQUET'S TEST IN PULMONARY TUBERCULOSIS F  
SCHEURLEN, Beitr z Klin d Tuberk **69** 59, 1928

The total protein content varies so much as to be clinically insignificant. The albumin-globulin ratio depends on the extent of the disease, the degree of destructive processes and the activity. Its determination may complete, but never substitute, a thorough clinical examination. The albumin-globulin ratio and the speed of sedimentation of the red cells are fairly parallel. They do not undergo any marked and definite alterations during a period of four months, while the Pirquet test increases in intensity in almost all active and nonprogressive cases.

MAX PINNER

TUBERCLE BACILLI STAINED BY THE METHODS OF ZIEHL-NEELSEN AND MUCH  
K HAGEDORN, Beitr z Klin d Tuberk **69** 166, 1928

There are types of tubercle bacilli which cannot be demonstrated by Ziehl's stain, but only by Much's stain. A part of these take up the carbolfuchsin if they are first stained by Much's method. This property is retained if the bacilli are alternately stained according to the methods of Much and Ziehl.

MAX PINNER

THE CULTIVATION OF TUBERCLE BACILLI OF LOW VIRULENCE, PARTICULARLY OF B C G, IN THE CORNEA O. KIRCHNER, Beitr z Klin d Tuberk 69 181, 1928

Tubercle bacilli of low virulence can be cultivated in serial passage in the cornea. This method excludes the possibility of spontaneous infection with another strain. This method will eventually permit the decision of whether or not the B C G strain retains its low virulence in continuous animal passage.

MAX PINNER

ANIMAL INOCULATION IN SURGICAL TUBERCULOSIS M. KNORR and H. FRILDRICH, Beitr z Klin d Tuberk 69 385, 1928

Animal inoculation is the most reliable diagnostic method in surgical tuberculosis. It yields better results than the histologic examination of excised tissue. After intraglandular injection, the diagnosis could be made within four weeks in more than 85 per cent of cases.

MAX PINNER

BARTONELLA ANEMIA OF RATS V. SCHILLING and A. S. MARTIN, Klin Wchenschr 7 1167, 1928

The etiologic relationship of *Bartonella muris* (Mayer) was confirmed. Among thirteen splenectomized rats, two were found immune to splenectomy and inoculation. Of seven inoculated rats without splenectomy there were only four immune, the other three were infected with *Bartonella* blood or by cultures. Abundant growth was obtained once on blood agar, and the cultures were highly infectious. Six *Bartonella* rats, that spontaneously recovered after splenectomy, were reinfected either by blood transfer or by culture, and, accordingly, were not immune.

Morphologically and clinically, *Bartonella muris* differs markedly from *Bartonella bacilliformis* of Oroya fever and from the rod-like structures ("Erythronkonten Schillings") of pernicious anemia.

AUTHORS' SUMMARY

MENINGITIS IN CHILDREN CAUSED BY KOCH-WEEKS BACILLI H. MEYER and R. STEINERT, Munchen med Wchenschr 75 945, 1928

The symptoms, the clinical progress and the results of bacteriologic studies of three children with meningitis caused by Koch-Weeks bacilli are reported. None recovered, and the results of the postmortem examination of the brain of two are given. Both had a marked suppurative meningitis.

E. F. HIRSCH

TETANUS BACILLI IN GANGRENE OF THE LUNGS WITHOUT TETANUS SYMPTOMS W. VOIGT, Munchen med Wchenschr 75 994, 1928

Necrotic tissue from a gangrenous portion of the lung obtained by postmortem examination was examined in stained preparations and found to contain tetanus-like organisms. By cultures and animal tests, *B. tetani* was identified. The blood serum was not tested for tetanus antitoxin and it was not possible to explain the absence of symptoms of tetanus.

E. F. HIRSCH

STOOL EXAMINATION OF 500 PHILIPPINE SCHOOL CHILDREN L. LISSNER, Munchen med Wchenschr 75 1163, 1928

The total percentage of infestation by nematode parasites is 92.6. Of these, 16.4 per cent were *Anchylostoma duodenale*, 7.3 per cent *Ascaris lumbricoides*, 32.3 per cent *Trichocephalus dispar*, and 7.6 per cent *Oxyuris vermicularis*. An infestation with two varieties of parasites existed in 28.8 per cent. The ages of the children ranged between 8 and 18 years, those in the tenth to thirteenth years were most frequently infested. Unsanitary conditions of living are held responsible for the high percentage of infestation.

E. F. HIRSCH

BACILLUS ABORTUS OF BANG AS A CAUSE OF A SEPTIC DISEASE IN HUMAN BEINGS HORST HABS, Ztschr f klin Med **108** 445, 1928

*Bacillus abortus* was described by Bang in 1897, and since was considered as being pathogenic only for animals. It is transmitted in cattle by the genital route and also by mouth when animals are fed on grounds soiled with this germ. Habs reports four cases in which the bacillus was isolated from the blood of patients in whom it caused a peculiar septicemia resembling somewhat that of undulant fever. The author is emphatic, however, that in these cases it concerned *Bacterium abortum* Bang and not *Bacterium melitensis* Bruce, basing his opinion on epidemiologic and serologic data. He also believes that the disease in human beings is apparently less rare than it is believed, being transmitted with the milk of cows. Four clinical histories of patients with this disease are given in detail, accompanied by a comprehensive discussion.

B. M. FRIED

THE POTENTIAL ALKALESCENCE OF THE BLOOD AND ITS FLUCTUATIONS IN PULMONARY TUBERCULOSIS T. D. KAHN, Ztschr f Tuberk **50** 480, 1928

The potential alkalescence of the blood in pulmonary tuberculosis is usually decreased. This decrease is roughly parallel with the extent and activity of the process. During exacerbations, hyperalkalosis is observed, followed by hypoalkalosis. Both rapid decrease and rapid increase in the alkalescence of the blood is prognostically an unfavorable sign.

MAX PINNER

EXPERIENCES WITH THE SEDIMENTATION REACTION OF ERYTHROCYTES H. STARCKE, Ztschr f Tuberk **50** 486, 1928

The prognostic and diagnostic evaluation of the sedimentation reaction must be made with great caution. The increase in the sedimentation rate, following a diagnostic injection of tuberculin, is not regular, it depends more on the dosage of the tuberculin than on the activity of the process. The fluctuations of the sedimentation rate do not give a reliable indication for tuberculin therapy.

MAX PINNER

THE BLOOD PICTURE IN HUMAN TRICHINIASIS W. BEHR, Folia haemat **36** 25, 1928

In four cases of trichiniasis, the blood showed constantly a high eosinophilic count. In two instances an eosinophilia of 14 and 11 per cent, respectively, was present in the blood three months after an apparent recovery.

B. M. FRIED

SPONDYLITIS DUE TO BACTERIUM ABORTUS L. P. JENSEN, Hospitalstid **71** 637, 1928

In Jensen's patient with an abscess in the left groin, a history of febrile disorder, diagnosed as typhoid a year earlier, and exposure to possible infection with *Bacterium abortum*, roentgen examination disclosed marked neoformations of the bones and destructive processes in the third and fourth lumbar vertebrae. Tuberculosis was excluded. While the roentgenographic observations resembled those in spondylitis typhosa, typhoid bacilli were not found at the time or on repeated tests since, but a definite serologic reaction to Bang's abortion bacillus was established after ten months of treatment.

BACTERIOPHAGES IN CHICKEN EMBRYOS TAGE KEMP, Acta path et microbiol Scandinav **5** 105, 1928

A large number of publications deal with the search for bacteriophage lytic principles in embryonal organs of fowls and calves, and in human fetuses, though the writers have not succeeded in demonstrating them. In the experiments described in this paper, lytic principles were found in chicken embryos in a number



of cases. An attempt was first made to provoke the formation of lysins in a *Bacillus coli* strain by adding to the broth cultures of the strain varying quantities of coal-tar together with coal-tar and embryo chick tissue simultaneously, by these means, lysins were not formed in the *B. coli* cultures, but lysins were accidentally found in some of the chicken fetuses in the preparatory experiments for this series of tests. A number of embryo chicks were extracted from the eggs under sterile conditions and cut with scissors into 3 by 4 pieces, each piece was placed in a test tube containing common peptone broth and incubated for forty-eight hours at 37 C, without the appearance of any growth. A drop of *B. coli* culture was added to each tube, and, after twenty-four hours in the thermostat, the broth was filtered through a Seitz asbestos filter. Seven of the resulting filtrates contained active lytic principles against coli bacilli. Using special quantitative methods, which are described, the authors examined the relations of the seven lysins, when tested on colon, typhoid and dysentery strains, and proved that the lysins could be divided into three groups, showing outstanding differences in their action on the three strains of bacteria. Later information revealed the fact that the embryos from which the lysins had been isolated were derived from eggs from a poultry farm attacked by an epidemic of so-called white diarrhea, in a later examination of a large number of embryos (about 100) from eggs derived from healthy fowls, lysins could not be demonstrated in the embryos, it is therefore reasonable to connect the finding of lysins with the infectious disease prevailing in the poultry farm from which the eggs originated. It is difficult to bring these observations into harmony with the theory that the bacteriophage lytic principle is an ultramicroscopic virus.

AUTHOR'S SUMMARY

THE ETIOLOGY OF ACTINOMYCOSIS IN DOMESTIC ANIMALS H. MAGNUSSON,  
Acta path et microbiol Scandinav 5 170, 1928

A large number of cases of so-called actinomycosis in cattle and swine has been studied. Under actinomycosis are classed suppuration with granulation tissue in the pus of which are characteristic granules with a peripheral layer of clubs. Of the cases examined in cattle, 41 per cent were found to be due to streptothrix, and in the cases of actinomycosis of the udder of swine streptothrix was found in 66.3 per cent. In a number of cases, the causative organism appeared to be staphylococci. Actinomycosis should be regarded as a chronic inflammation due to certain pyogenic bacteria, having the power to adapt themselves and form cell colonies with their own intercellular substance and protective sheath and then live in symbiosis with their host. To Magrou, the naturalist, must be given the credit of having proved by comparative studies of botryomycosis and actinomycosis the identity of these diseases and of having given the best biologic explanation hitherto of the origin and character of the infection.

### Immunology

ISO-AGGLUTININS IN THE NEW-BORN C. H. SMITH, Am J Dis Child 36 54,  
1928

It was observed, in 49.2 per cent of seventy-one cases of new-born infants, that the cord blood contained the full amount of receptors and iso-agglutinins so as to place it in one of the four designated groups. An increase in this percentage takes place during the first year of life.

An examination of the cord blood after an interval of ten days showed either a decrease in their titer or a complete disappearance in twenty-seven of the forty-one cases.

The iso-agglutinins of the cord and maternal blood have a qualitative similarity. Simple blood dilution does not seem to be the causative factor in the loss of iso-agglutinin strength following birth. The author is of the opinion that the similarity of iso-agglutinins of the child and mother and their subsequent diminution in the child following birth point to a transfer by way of the fetal circulation.

The author cites two cases in which, after primary demonstration of iso-agglutinins, a subsequent disappearance occurred. Later the specific blood group of the infant was established by the appearance of an agglutinin and associated iso-agglutinin. Thus the cord blood possessed both iso-agglutinins and could be placed in group O. The blood groups developed by the infant were A and B, respectively. Therefore, in establishing paternity by the iso-agglutinin reaction, it would be wise to wait until the permanent iso-agglutinins are developed.

The type of labor does not seem to have any effect on the placental transmission of iso-agglutinins.

H E LANDT

ABSORPTION OF UNDIGESTED PROTEINS IN HUMAN BEINGS H SUSSMAN,  
A DAVIDSON and M WALZER, Arch Int Med **42** 409, 1928

Subjects used in this study were given passive local sensitization by the intradermal injection of serum from an egg-sensitive patient. An egg meal was given the following morning, and the time noted as to appearance of reaction in the sensitized area. Of thirty-four subjects tested, 85 per cent reacted positively, and 78 per cent of the reactions occurred in the first hour. With fish proteins previously tested, 86 per cent of the reactions occurred in the first thirty minutes. Giving the test protein on a full stomach showed the reaction time. Peptone feeding did not exert any consistent effect on the time or severity of the reaction. On rectal injection, absorption of the protein occurred to a less extent than in the upper digestive tract.

HAMILTON R FISHBACK

PRODUCTION OF ACTIVE IMMUNITY AGAINST THE FATAL OUTCOME OF EXPERIMENTAL FECAL PERITONITIS B STEINBERG and H GOLDBLATT, Arch Int Med **42** 415, 1928

Eleven dogs were immunized by repeated intraperitoneal injection of living colon bacilli. Ten of these survived the intraperitoneal injection of a dose of feces proved to be lethal for normal dogs. Of eight dogs immunized by the intraperitoneal injection of colon bacilli killed by heat, only three survived the normal lethal dose of feces. Feces heated to 60 C for one hour proved sterile on culture, and did not produce peritonitis when injected into the peritoneal cavity of dogs.

HAMILTON R FISHBACK

SKIN SENSITIVITY OF RHEUMATIC SUBJECTS TO STREPTOCOCCUS FILTRATES E I M IRVINE-JONES, Arch Int Med **42** 784, 1928

Fifty-six strains of streptococci were isolated from the upper respiratory tracts of rheumatic children, and twenty-four strains from nonrheumatic children. No significant difference in regard to source was found in fermentation, neutralization and skin tests on rheumatic and nonrheumatic children. Patients followed for a period of time showed alternation of positive and negative phases of the skin reaction similar to experimentally produced allergy. Some of these had recurrent rheumatic attacks. Skin reactivity was found to be most marked in rheumatic subjects, especially in the acute stages. Circulating toxins were not found in the blood of acutely sick rheumatic persons. It is suggested that rheumatic fever is a form of allergic response to common streptococci.

HAMILTON R FISHBACK

BLOOD GROUPING OF BAFFIN ISLAND ESKIMOS PETER HEINBECKER and  
RUTH H PAULI, J Immunol **15** 407, 1928

The blood groupings of 166 Eskimos of Baffin Island are recorded. Further evidence is presented to support the view that the pure blooded Eskimo falls into blood group I.

AUTHORS' SUMMARY

STUDIES ON THE ANTIGENIC PROPERTIES OF THE ULTRAVIRUSES E W  
SCHULTZ and J HOYT, J Immunol **15** 411, 1928

No evidence of specific complement-fixing antibodies against the virus of herpes was found in the serum of rabbits which had been immunized by different routes with virus-brain suspensions. These immune serums also failed to present any evidence of specific precipitating antibodies. Virulicidal antibodies were demonstrable in all of the immune serums tested for this property.

AUTHORS' SUMMARY

THE PRIMARY TOXICITY OF GOAT-SERUM JOSEPH D ARONSON, J Immunol  
**15** 465, 1928

Fresh unheated normal goat-serum is hemolytic for guinea-pig erythrocytes, it is toxic when introduced into the general circulation or into the peritoneal cavity of normal guinea-pigs, it produces necrosis when injected into the dermis of normal guinea-pigs. The hemolytic, toxic and necrotizing action is dependent on a thermolabile and a thermostable fraction. The thermolabile fraction reacts in the same way as complement. After it has been removed from goat-serum the addition of fresh complement restores the hemolytic and toxic action but not the necrotizing action. The thermostable fraction is absorbed by certain tissues of the guinea-pig but not by the tissues of animals insusceptible to the action of goat-serum. Antigoat-serum neutralizes the hemolytic, toxic and necrotizing action of goat-serum. This neutralization is not brought about by complement fixation, but is brought about by the action of antibody on the antigen. Repeated injections of fresh goat-serum into normal guinea-pigs produce immunity to its necrotizing action, accompanied by the Arthus phenomenon. The appearance of the Arthus phenomenon is part of the process of immunity, it is not a result of the necrotizing action of the fresh goat-serum for it follows also injections of goat-serum from which the necrotizing property has been removed by heating. The hemolytic, toxic and necrotizing action of goat-serum is due to a single substance, which acts as a toxin.

AUTHOR'S SUMMARY

IMMUNITY TO BOTULINUM TOXIN MARY NEVIN and ELIZABETH LEE HAZEN,  
J Immunol **15** 489, 1928

Rabbits can be immunized by injection, intradermal and intravenous, of anti-toxin followed by toxin. Immunization by mouth or rectum did not succeed.

THE INCREASED SUSCEPTIBILITY OF THE ALBINO RAT INFECTED WITH THE  
TUBERCLE BACILLUS TO TUBERCULIN M I SMITH, Pub Health Rep  
**43** 2817, 1928

The object of this work was to ascertain the degree of increased susceptibility to tuberculin of rats infected with tubercle bacilli over normal animals, and the manner in which this is influenced by a diet deficient in vitamin A. The tuberculin preparation used was a water soluble powder suitable for intravenous injection, made from a synthetic nonprotein medium on which the bacilli had grown for six weeks. Rats on adequate and deficient diets were inoculated intraperitoneally with human tubercle bacilli, a procedure which has no appreciable effect on normal animals for several months. At varying intervals thereafter, the effect of the tuberculin preparation injected intravenously was determined. The minimum lethal dose for rats on the adequate diet was 300 mg per kilogram for noninfected and 50 mg per kilogram for infected animals. The ratio of susceptibility to tuberculin of the infected compared with the normal animal was therefore roughly 6 to 1. In animals suffering from vitamin A deficiency, the ratio was about 40 to 1, indicating that hypersensitiveness is increased sevenfold by the deficient diet. Hypersensitiveness was evident fourteen days after infection, and reached its height at thirty days. The same effect was produced by bovine as by human bacilli, but not by killed organisms.

It was concluded that invasion of the tissues of the rat by tubercle bacilli effects an increased susceptibility to tuberculin, as occurs in the more susceptible animals, and that the systemic effects of tuberculin are only quantitatively different in the tuberculous and the normal animal

THE IN VITRO TITRATION OF *B. WELCHII* ANTITOXIN BY ITS ANTIHAEMOLYTIC POWER J H MASON and A T GLENNY, J Path & Bact **31** 629, 1928

Identical results are obtained for *B. welchii* antitoxin by antihemolytic titration in vitro and by antitoxic titration in vivo by intravenous injection into mice

AUTHORS' SUMMARY

THE RELATION OF AGGLUTINATION BY SPECIFIC SERUM TO AGGLUTINATION BY ACID J A ARKWRIGHT, J Path & Bact **31** 665, 1928

There are two agglutinable substances in a culture of motile bacteria of the *B. typhosus*, Salmonella group, which are responsible for agglutination by acid at different zones of hydrogen ion concentration or ( $H^+$ ) and these substances are probably identical with the flagellar and somatic antigens, respectively, which react with H and O agglutinating serums

THE ACTION OF IMMUNE SERUM ON VACCINIA AND VIRUS III IN VITRO C H ANDREWES, J Path & Bact **31** 671, 1928

Immune serum does not destroy vaccinia virus in vitro, even after twenty-four hours' contact at room temperature. The inactivation of the virus is not associated with any stable antigen-antibody union occurring in vitro in twenty-four hours at room temperature. There is at present no evidence that any in vitro antigen-antibody union at all is involved. These conclusions are also applicable to virus III, though owing to greater difficulties in its study the evidence is less complete.

AUTHOR'S SUMMARY

THE RELATIONSHIP BETWEEN THE BACTERICIDAL POWER OF NORMAL GUINEA-PIG SERUM AND COMPLEMENT ACTIVITY JOHN GORDON and ARTHUR WORMALL, J Path & Bact **31** 753, 1928

The conclusion is reached that hemolytic complement and bactericidal complement have a similar constitution and are probably identical. Thus the bactericidal system investigated here appears to consist of an immune body (present in normal guinea-pig serum) and complement.

FIXATION OF COMPLEMENT BY *B. TYPHOSUS* AND NORMAL GUINEA-PIG'S SERUM ERNEST M DUNLOP, J Path & Bact **31** 769, 1928

Guinea-pig's serum shows zonal fixation of its hemolytic complement in the presence of a suspension in saline of the majority of strains of *B. typhosus*. Different strains of *B. typhosus* vary in their ability to cause zonal fixation of guinea-pig's complement. Two of twenty-one strains examined have failed to do so. The phenomenon is explicable on the basis of the presence in normal guinea-pig's serum of a natural antibody. This resembles immune antibody in its ability to sensitize the organisms, so that they can then fix complement, but it differs from immune antibody in its thermolability and in its comparative lack of specificity. This antibody varies greatly in its sensitiveness to heat and it is sometimes more labile than complement. *B. typhosus* unites with the antibody at 0 C, usually thereby becoming sensitized, but no fixation of complement occurs at 0 C. The antibody can be removed from guinea-pig's serum not only by organisms with which it reacts specifically (leading to complement fixation) but also by other organisms, and by agents such as coal dust charcoal or powdered glass. Hemolytic complement can be removed from guinea-pig's serum without

destruction of the antibody. Certain other organisms (coliform bacilli, anthracoid bacilli and staphylococci) also cause zonal fixation of guinea-pig's complement. The addition of heated normal serum (rabbit's or human) to mixtures of typhoid bacilli and guinea-pig's complement sometimes inhibits, sometimes increases, the zone of complement fixation.

AUTHOR'S SUMMARY

REPORT OF THE ROYAL COMMISSION OF INQUIRY INTO FATALITIES FROM TOXIN-ANTITOXIN AT BUNDABERG CANBERRA, M. J. Australia 22 and 38, 1928

Of twenty-one children injected with toxin-antitoxin on Jan. 27, 1928, some with the initial and some with the second dose, eighteen became ill and twelve died. The same bottle had been used several times previously without untoward effects. The symptoms were similar in all the fatal cases, beginning from five to eight hours after injection with vomiting and diarrhea, fever, rapid pulse, cyanosis and circulatory failure. The deaths occurred in from fifteen to thirty-four hours. The survivors developed abscesses at the site of inoculation. The most significant postmortem observation was degenerative change of the lymphoid tissue throughout, suggestive of the action of a toxic agent in the blood stream. Changes peculiar to the action of diphtheria toxin, such as fatty degeneration of the heart muscle or hemorrhages, were not found. Examination of the remaining toxin-antitoxin mixture showed it to be cloudy on the following day, and staphylococci were cultivated both from it and from the abscesses. No evidence of tetanus or of free toxin was found in the mixture, and injections of antitoxin in the sick children had no effect. The symptoms and pathologic observations pointed to a staphylococcus infection as the most likely cause of the illnesses, in spite of the rapidity of the deaths and absence of metastatic abscesses in the survivors. The organism was not highly pathogenic for laboratory animals, except for the rabbit. Skin tests in human beings with a filtrate produced marked reactions in some persons and none in others, suggesting a possible explanation of the failure of some of the children to react.

The batch of toxin-antitoxin in question was issued without addition of a preservative, and the bottle was kept at room temperature, so that conditions were favorable for the multiplication of organisms. There were two possible sources of contamination. The needles used for the injections were lifted out of sterile water with the fingers instead of with forceps, and air was necessarily injected onto the rubber-capped bottle as the fluid was removed. Although the fingers of the operator appeared to be the most likely source of the staphylococci in this case, an experiment was made to investigate the latter possibility. Air was injected and fluid removed with sterile needles in the usual manner from a number of rubber-capped bottles of toxin-antitoxin without antiseptic, and 30 per cent of them were found to be contaminated in this way. No contamination occurred in the presence of an antiseptic.

The commission concluded that the deaths were due to staphylococci with which the mixture was contaminated during the first injections made from the bottle, and that the repeated use of material from a rubber-capped bottle containing no antiseptic is dangerous. It recommended that biologic products in which growth is possible should not be issued in this form, and that all products not containing an antiseptic should be so labelled with the warning that they must be completely used at one time or the remainder discarded. Special training for those engaging in the immunization branch of public health work was advised.

BEATRICE R. LOVETT

LOCAL VACCINATION AGAINST RABIES P. REMLINGER and J. BAILLY, Ann de l'Inst. Pasteur 42 349, 1928

Using a series of guinea-pigs as test animals, attenuated rabies virus was locally inoculated by means of friction on the skin. Subsequent attempts to produce localized or general infection demonstrated a degree of immunity. The

practical value of strictly local immunization is discountenanced, but the doctrinal value in showing an affinity of the virus for the skin is upheld

M S MARSHALL

BLOOD GROUPS IN MAN AND CHIMPANZEE JEAN TROISIER, *Ann de l'Inst de Pasteur* **42** 363, 1928

The red blood cells of fourteen chimpanzees are agglutinated by human serums III (B) and IV (O), the human serums (AB) I and II (A) are without effect. The serum of the chimpanzees agglutinates human cells I (AB) and III (B). It is without effect on human cells II (A) and IV (O). The blood of chimpanzees possesses hemagglutinins (agglutinin A and agglutinin b) of group II of man. The quantity of agglutinin and especially of agglutinins varies moderately in subjects, or from day to day in the same subject. The test of saturation of agglutinins does not enable one to distinguish the blood of man II (A) from the blood of the chimpanzees. Man II may receive with impunity intravenous injections of citrated chimpanzee blood. This humoral and cellular identity between the chimpanzee and man II favors the phylogenic hypothesis of a common ancestor.

AUTHOR'S CONCLUSIONS

ALLERGY AND CLASSIFICATION OF PULMONARY TUBERCULOSIS W CURSCHMANN, *Beitr z Klin d Tuberk* **69** 501, 1928

The determining factor in the development of tuberculous lesions is the immunity and not the allergy. The immunity can be determined by tuberculin skin reactions with study of the blood picture. Positive allergy and absence of shifting to the left, with normal sedimentation time, indicates high immunity, while positive skin tests, with shifting to the left and increased sedimentation rate, indicate lowering of the immunity. It is necessary to indicate the gross anatomic character of the lesions such as, infiltration, dissemination, cavity, cirrhosis, type and extent of the lesion and its tendency toward progression, cavitation or retrogression. It is not necessary to create definite pictures of tuberculosis, and attempts at histologic classifications are futile and unnecessary.

MAX PINNER

IMMUNIZATION OF GUINEA-PIGS WITH SAPONIFIED TUBERCLE BACILLI K W CLAUBERG, *Beitr z Klin d Tuberk* **69** 551, 1928

Tubercle bacilli were saponified by 10 per cent potassium hydrate and exposure to heat. The final product was neutralized with lactic acid. Ten of twelve animals which were vaccinated with this preparation proved to be refractory to a subsequent infection, one developed some tuberculosis and one died of generalized tuberculosis. Four of the controls did not develop tuberculosis and five died of generalized tuberculosis three months before the completion of the experiment.

MAX PINNER

INCREASE OF FLOCCULABILITY IN THE SERUM IN TUBERCULOSIS J VON DARANYI, *Beitr z Klin d Tuberk* **69** 558, 1928

This is a review of the literature dealing with the serum reaction known under the author's name.

MAX PINNER

SPECIFIC-PROTEOLYTIC FERMENTS IN THE SERUM IN PULMONARY TUBERCULOSIS F LASCH and R GROSS, *Beitr z Klin d Tuberk* **69** 670, 1928

Abderhalden's test was done on a small series of patients. The antigen was prepared from tubercle bacilli by boiling and extraction with lipid solvents. Forty-six of sixty patients with pulmonary tuberculosis reacted positively. Three of fifteen healthy persons reacted positively. Pregnancy of not more than three months' standing did not interfere with the specificity of the reaction.

MAX PINNER

THE VIRULENCE OF B C G S L LANGE and K W CLAUBERG, Beitr z Klin d Tuberk **70** 346, 1928

The BCG strain, even in massive doses, is but little virulent for guinea-pigs. The specific alterations which it produces remain localized and disappear again. The strain can be isolated from infected animals but neither the pure culture nor the infected organs produce any changes on reinjection into animals. The pathologic action of this strain could not be enhanced by submitting the animals to injuries, such as exposure to cold, inhalation of dust, vitamin deficient food, injection of sodium aurothiosulphate, injection of diphtheria toxin and mixed infection.

MAX PINNER

THE COMPLEMENT FIXATION IN TUBERCULOSIS M STEIN and SCHACHS-  
WARLY, Beitr z Klin d Tuberk **70** 408, 1928

In a series of 136 patients complement fixation was done with the antigens of Wassermann, Klopstock and Neuberg and with an antigen of nonacid-fast organisms grown in saponin containing glycerol broth. The latter antigen gave the best results. But only 40.4 per cent of patients with clinical tuberculosis reacted positively, and 5 per cent of nontuberculous patients reacted positively.

MAX PINNER

THE USE OF SERUM OBTAINED AFTER DEATH FOR ISO-AGGLUTINATION  
P SEREBRANIKOFF and M LEITSCHICK, Ztschr f d ges Gerichtl Med  
**12** 496, 1928

Blood from the corpse gives good serum for iso-agglutination if obtained not later than seventy-two hours after death. Chronic diseases and injuries of the liver may be unfavorable for securing good serum. One drop of 20 per cent solution of formaldehyde to 2 cc of serum is recommended as a preservative.

INVESTIGATIONS OF RELAPSE STRAINS OF TRYPANOSOMES BY MEANS OF THE  
RIECKENBERG PHENOMENON F LEUPOLD, Ztschr f Hyg u Infektions-  
krankh **109** 144, 1928

The Riekenberg phenomenon consists in agglutination of the blood platelets around the trypanosomes, when the blood of a mouse recovered from a trypanosome infection is mixed with blood containing organisms of an identical strain. No agglutination takes place with heterologous strains. The reaction has been shown to depend, not on the platelets themselves, but on antibodies present in the serum of the immune animals. The author found that immune serum could be injected into normal animals and their blood used for the reaction.

"Relapse strains" of trypanosomes were obtained by allowing mice infected with an original strain to recover partially (by giving insufficient doses of arsphenamine), and taking their blood during the subsequent relapse. Strains taken from different animals during their first relapse behaved like heterologous strains. Frequently no agglutination was observed when organisms from one animal were mixed with blood from another. It appeared, however, that the number of different strains obtainable from relapses was limited. Thus 56 per cent of the relapse organisms corresponded to one type, 20 per cent to a second, 20 per cent gave positive agglutination reactions with immune blood of both types, and 4 per cent with neither. The author concludes that the blood platelet reaction can be used in this way to identify and differentiate strains of trypanosomes. The results agreed with those obtained with the reinfection method, in which it is found that immune animals can be reinfected with heterologous but not with homologous strains.

B R LOVETT

EXPERIMENTAL IMMUNIZATION WITH BCG H CHIARI, N NOBEL and A SOLE,  
*Ztschr f Tuberk* **51** 354, 1928

Following the administration of BCG by mouth, guinea-pigs usually do not develop tuberculous alterations, probably because the bacilli are excreted with the feces. Pure subcultures from the original BCG vaccine are virulent for guinea-pigs. Intraperitoneal immunization does not confer immunity to guinea-pigs. Most, but not all, of the treated animals lived longer than the controls after infection with fully virulent bovine bacilli.

MAX PINNER

ATTEMPTS TO IMMUNIZE RABBITS WITH SYPHILITIC TESTICULAR TISSUE  
M HONDA, *Acta Dermatologica* **12** 179, 1928

Male rabbits were injected in various ways with emulsions of rabbit testicles rich in virulent spirochetes, but no demonstrable evidences of immunity were obtained.

### Tumors

PRIMARY NEOPLASMS OF THE HEART, REPORT OF AN UNUSUAL CASE ERNEST  
B BRADLEY and ELMER S MAXWELL, *J A M A* **91** 1352, 1928

The growth, which is regarded as primary in the heart, occurred in a man, aged 62. There were numerous metastases.

THE MALIGNANT FUNCTIONS OF THE CHORIONIC EPITHELIUM W BLAIR BELL,  
*J Obst & Gynec Brit Emp* **35** 233, 1928

Evidence is presented to show that the chorionic epithelium resembles malignant tissue of somatic origin in its function and chemical constitution. The high phosphatid-cholesterol ratio necessary for permeability of the cell membrane to water soluble foodstuffs and to the high water content of the cells is more pronounced in the trophoblast than in malignant tissue by its function of glycolysis in aerobic as well as in anaerobic conditions. There is a lower dextrose content and a higher lactic acid content in the placental circulation than in the normal venous circulation of the mother. This might indicate that, in regard to glycolysis, the chorionic epithelium functions like a malignant growth. Like malignant neoplasms, the chorionic epithelium shows a  $p_H$  value on the acid side of neutrality which is more pronounced in the younger placentas.

A J KOBAK

MIXED TUMORS OF THE UTERUS AND VAGINA WILFRED SHAW, *J Obst & Gynec Brit Emp* **35** 498, 1928

Mixed tumors of the female genitalia are classified according to their anatomic origin as follows: uterine, cervical and vaginal. Those arising from the body of the uterus are the rarest, there being only thirteen cases on record. The growth is polypoid and quite vascular, but its most dependent part is usually necrotic. The tumors develop after the menopause. Mixed tumors of the cervix occur at the average age of 34 and usually have a grapelike form. The mixed vaginal tumors are found in young children or infants and are usually polypoid. Mixed tumors are malignant and in association with sarcoma cells, they contain striated embryonic muscle cells, cartilage, fat, bone and elastic tissue. The author pointed out that the gelatinous matrix was similar to embryonal mesenchyme but, on the whole, he admitted that there is no satisfactory explanation of the origin of these tumors.

A J KOBAK

ATTEMPT TO TRANSMIT CANCER OF THE HUMAN DIGESTIVE TRACT TO THE  
CHIMPANZEE JEAN TROISIER and HENRI LIMOUSIN, *Ann d l'Inst Pasteur*  
**42** 380, 1928

The authors report that the results thus far are not successful.



THE HYPOPHYSIS AND DIFNCEPHAI ON IN CARCINOMA FRIEDRICH WOHLWILL,  
Deutsche Ztschr f Nerven 105 63, 1928

Only 5 of 177 cases of carcinoma showed metastasis in a hypophysis. Most of these were primary tumors of the breast. In 45 of 177 cases, instead of emaciation, a normal general physical condition or increase in weight were found. Discarding those cases in which the influence of other endocrine glands, notably the ovary, was suggested, the author accounted for eighteen cases on the bases of lesions in the hypophyseal-diencephalic vegetative centers.

CYTOCHROME IN TUMOR TISSUE H. YACR, H. TAMURA and W. NAKAHARA,  
Japan M. World 8 233, 1928

We examined four types of transplantable tumors for the occurrence of cytochrome, an intracellular respiratory pigment recently discovered by Keilin, and found that Fujinawa rat sarcoma contains a large amount, Flexner-Jobling rat carcinoma and Bashford mouse carcinoma a medium amount, and Rous chicken sarcoma either small or no demonstrable amount of this respiratory pigment. It is probable that these facts can be correlated with the difference in the ability of different types of tumors to withstand the deprivation of oxygen.

AUTHORS' SUMMARY

### Medicolegal Pathology

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AUTHOR'S SUMMARY

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Most of these metallic objects were carried along in the blood current through the heart into the lungs where they caused little trouble when sterile. The migration often required days. The experiments were made with fourteen dogs, and all but three of ninety-four of the foreign bodies introduced into the veins passed on into the lungs. These results in dogs are somewhat different from observations on the transportation of missiles in the veins in human beings, for as a rule after their arrival in the heart they usually remain there and are not forced out into the lungs.

E. R. LE COUNT

TRAUMA OF THE CAUDAL REGION OF THE SPINE H. KELLER, Internat Clin 2 58, 1927

With a good account of the relation of the coccyx to the many muscles and nerves of that region, seven cases of injury of the coccyx are reported: one with posterior dislocation, one with partial fracture from the sacrum and five with

sprains Six of the patients were women, and one was a man The pain at the time of injury is so severe that fainting is not uncommon It radiates down the thighs and may extend up the trunk and even into the arms Frequent urination and pain with defecation are symptoms Much more aid to correct diagnosis is obtained by palpation than by roentgen examinations, for the coccyx is not bony By conservative treatment recovery generally occurs Laparotomy had been urged for two of the seven patients, and for two others removal of the coccyx All recovered without operation

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UNSUSPECTED FOREIGN BODIES IN THE CRANIUM A FRIBOURG-BLANC and H DURAND, *Ann de med leg* 8 148, 1928

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The enrichment of medical experience from great wars does not all take place during the period of conflict It is certainly prolonged over the life of those who survive injury, and probably much longer This fact is being demonstrated from time to time by opportunities to reexamine old injuries, by examinations made for the revision of pension awards, and by serious or fatal sequences which first appear years after injury Two such late results, one concerned with an extensive trephining, the other with abrupt unexpected death probably from an abscess of the brain following injury requiring enucleation of one eye, were reported by Fribourg-Blanc (*Ann de med leg* 7 52, 1927)

His more recent report with Durand of foreign bodies in the head is remarkable It arose from systematic radioscopic examination of the heads of fifty exsoldiers in the neuropsychiatric service of the Military Hospital, Val-de-Grace, in Paris Foreign bodies were found in the heads of thirty, and entirely unsuspectedly in all but one These were intra-orbital, nineteen in the soft parts or bone and eight intracranial In this last group there were six metallic foreign bodies

Belot mentions a soldier with a missile in one buttock after it had passed through the trunk lengthwise from its entrance behind one shoulder as he was prone, a certificate possessed by another stated that he carried a piece of shrapnel in his right lung, but the fragment was found near the hip In several persons the discovery of particles of glass was made some time after the wounds had healed More interesting than these were intracardiac foreign bodies found in the hearts of three men, two seen during the war, all had entered from in front and lodged in the right ventricle They were so violently in motion with the blood that considerable ingenuity was required to find them radioscopically, a timing exposure to the short intervals was necessary to photograph them Examination of one of the soldiers after a year indicated a partial anchoring of the piece of metal None of the three men was aware of the presence of these foreign bodies, nor were they greatly discommoded

E R LE COUNT

EXPERIMENTAL VENOUS AIR EMBOLISM S FREY, *Arch f klin Chir* 148 536, 1927

Probably the oldest of the theories explaining death from the entrance of air into the systemic veins is the failure of an adequate blood supply to the higher "vital" centers in the brain, because the air passes through the lungs into the systemic arteries Another interpretation is distention of the right ventricle and auricle with froth so that blood is not forced through the lungs A third is the failure of blood to pass through the lungs, with a resulting internal asphyxia, which Frey believes accounts for the death of the dogs used in his experiments Air was put into the femoral veins, and what then happened depended largely on how much was injected and whether it was put in quickly or slowly With considerable air introduced rapidly, there were large bubbles in the blood and a marked drop in arterial blood pressure He found the pulmonary capillaries in dogs impermeable for air, but failed to observe any indications that cardiac paralysis occurred

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because of acute dilatation. With a patent foramen ovale, air may easily get through into the left auricle and then into the systemic arteries. Frey found the air in the lungs of the dogs on roentgen examination, but not in the heart. He urges that by surgical measures the air be withdrawn from the pulmonary artery in cases of air embolism, aspirated possibly with a syringe.

E R LE COUNT

ADIPOCERE S GOY, *Biochem Ztschr* **187** 470, 1927

The composition of adipocere from two bodies reported in 1922 is compared with the results of a chemical examination of this material recently obtained from a third body. In all of the material, the amount of free fatty acids was large, there was less olein than other fats. It is suggested that the low melting point of oleic acid may be connected with its disappearance.

E R LE COUNT

HEMOGLOBIN RESISTANCE AS AN INDEX OF THE AGE OF NURSINGS AND PREMATURELY BORN H BISCHOFF, *Deutsche Ztschr f d ges gerichtl Med* **11** 340, 1928

When all are used together, the many conditions by which the duration of gestation of new-born infants is estimated are fairly reliable. Among these are the weight, length of the nails, consistency of the skin and size of certain foci of ossification. But these have little value for determining the age some weeks or months after birth at term, although by some investigators considerable reliance is placed on the length and size of certain bones. Bischoff has used the resistance of the hemoglobin to alkalis not only to ascertain the age of prematurely born infants, but also to decide during the first year of their life the time of conception of prematurely born infants, if the date of their birth is known. These are matters of importance in connection with foundlings, illegitimacy and questions of parenthood. The method was described by Korber in 1866 and has been somewhat modified since. Its details are too involved to be given here. The age is learned to within a few weeks. The tests were made by Bischoff on the blood of 100 nurslings and 38 prematurely born infants. Fetal hemoglobin is more resistant to the action of alkali than is the hemoglobin of adults, and that of a prematurely born infant is also more resistant than is the hemoglobin of an infant of the same age born at term. It is of considerable interest that these tests can be employed with the hemoglobin of decomposed or dried blood even though it has been kept for several years. The tests have been useful in demonstrating birth at term of infants already dwarfed.

E R LE COUNT

SPONTANEOUS RUPTURE OF THE ESOPHAGUS RAESTRUP, *Deutsche Ztschr f d ges gerichtl Med* **11** 373, 1928

Explosive vomiting awakened a man early in the morning after a feast during which he ate considerable roast pig and sausage, and drank but little. The vomiting was followed by pain in the stomach radiating to the back. A diagnosis of perforated gastric ulcer was made, but when the abdomen was opened the stomach was found normal, death occurred about thirty-six hours after the feast. A tear on the right side of the cardiac end of the esophagus all the way through and 3 cm long and also two smaller superficial tears of the lining were found after death, in the left pleural cavity, there were two liters of turbid fluid. No disease or anomaly of the esophagus was found to help explain the rupture.

Spontaneous rupture of the healthy esophagus is one of the rarest conditions responsible for sudden death. It usually is caused by violent explosive vomiting after excessive eating. Spontaneous rupture of the diseased esophagus may also occur. Attacks of coughing, collapse, dyspnea, sweating, restlessness and a rapid and weak pulse are the symptoms, as a rule, but in the case reported by Raestrup the symptoms were abdominal.

E R LE COUNT

## PUNCTURE OF THE SUPERIOR LONGITUDINAL SINUS OF THE DURA IN INFANTS

L FABIAN, *Monatschr f Kinderh* **36** 390, 1927

Several deaths have resulted from needle wounds of the sinus or large cerebral veins made in the securing of blood or the administration of drugs intravenously, some from thrombosis and others from hemorrhage. Some deaths occurred because the patients were bleeders, others, because cerebral veins had been wounded accidentally and subdural hemorrhages produced. Some infants were atrophic and had myocardial degenerations. These conditions promote thrombosis in the dural sinuses where thrombosis is said to occur more easily than in other veins. Fabian believes that needle puncture of this sinus is dangerous and that indications for the procedure should be restricted.

E R LE COUNT

THE ORIGIN OF PARALYSIS AGITANS IN TRAUMA F LOTMAR, *Der Nervenarzt***1** 6, 1928

That paralysis agitans may be caused by injury is a relatively modern conception, and apparently is steadily gaining ground. But the number of cases for which it is believed trauma was responsible is still small. Two cases reported by Henssegge (*Ztschr f d ges Neurol u Psychiat* **110** 796, 1927) have been referred to in this section. There probably will be considerable interest in the account of two new cases by Lotmar, because the age of the patients was only 31 and 43 years, respectively, which is considerably earlier than the others previously observed. In the younger, the disease was not fully established until after a second fall, and in each the symptoms began within a few months after injury. The initial injuries were falls of from 11 to 14 feet. There is considerable difficulty in explaining how the paleostriatal changes peculiar to paralysis agitans in the aged and generally regarded as senile are produced by external violence, as a number of investigators have claimed that the changes in the basal ganglions are the same, whether the disease follows or has no possible connection with trauma.

E R LE COUNT

FATAL CRIMINAL SUBACUTE POISONING WITH THALLIUM L KAPS, *Wien klin**Wchnschr* **40** 967, 1927

A wife began to poison her husband in June by adding to his food "Zelio," a rat poison which owes its virtue to thallium sulphate. He came under observation in a Vienna hospital the next month where poisoning was suspected, improvement did not begin until he was denied food brought him from the outside. He was discharged on September 1, but returned in a much worse condition a week later and died, September 27. Although a medicolegal inquiry with postmortem and chemical examinations was made, it was not learned that death was caused by thallium until about two years later when the affair was reviewed in court.

About 30 Gm of thallium sulphate was given at intervals of about three months. The symptoms were much like those due to lead and to chronic poisoning with arsenic when the symptoms result mainly from damage to the nerves. There were cramps in the stomach and abdomen, stomach distress, retching and vomiting. The joints of the toes and fingers were painful, but not swollen or red. The soles of the feet were sore, the ankles swollen and at one time articular rheumatism was diagnosed. An eruption of the skin of the eyelids and cheeks with superficial necrosis, ulcerative blepharitis and edema of the face developed. Total alopecia of the scalp occurred. It was diagnosed "toxic defluvium." The abdomen was generally tender, as were the muscles of the extremities, especially the peroneal groups. Hypnotics were required for restlessness at night, and shortly before death there was extensive suppuration in the cutaneous lesions of the face, and the patient became blind and demented. It was thought that retrobulbar neuritis caused the blindness.

Small traces of arsenic were found chemically after death in portions of the body taken for examination, but thallium was not looked for. Haberda presented a long review of the poisoning (*Beitrag zur gerichtl. Med.*, 1928, vol 7). When thallium is added to the food of rats, it is asserted that calcium is removed from the bones and an alkalosis with hypochlorhydria or achlorhydria appears, also, disturbances of growth, testicular atrophy, changes in the lining of the stomach with the appearance of metaplastic stratified epithelium and hyperplasia and accumulation of heavily keratinized cells, alopecia and focal corneal opacities occur. It is also stated that children are less susceptible to thallium than adults. A few cases of acute poisoning in man with thallium have been reported. It is believed by Kaps that this is the first death from chronic poisoning with this rare metal. Thallium salts are chiefly used as depilatories. Organic compounds were first prepared a few years before this paper was written and have not yet gained extensive therapeutic use.

E R LE COUNT

MILIARY TUBERCULOSIS AND TRAUMA F ZOLLINGER, Wien med Wchnschr  
77 1281 and 1317, 1927

It has been known for a long time that, in those already tuberculous, the disease may develop in an active form where tissues are injured, especially in bones. From such secondary lesions systemic infection by the blood, miliary tuberculosis, often has its origin. Zollinger believes that this last outcome of injuries is rare. Of 85,623 persons whose injuries were reviewed because of insurance, the question of tuberculosis arose in only 157. Miliary tuberculosis followed injury in one of these patients. From other sources, Zollinger states that trauma caused systemic dissemination in only 3 of 789 persons who were ill from tuberculosis, and in only 2 of 7,822 with injuries received during the war.

His review and bibliography are splendid, and many reports from the literature are aptly used. Among these are reports of deaths from miliary tuberculosis caused by injuries which crushed a tuberculous kidney and tore adhesions in the chest where tuberculous granulation tissue had bound the lung to the chest wall, and in a third person a tuberculous gland was torn by unusual straining. In another report cited, the cause was exposure to cold when the patient was wet. There must be a definite sequence of events in order to attribute the tuberculosis to injury with assurance. The earliest death from miliary tuberculosis has occurred fourteen days after the injury and the latest, eight weeks. The average time required for symptoms of generalization to appear is from ten to twelve days.

When miliary tuberculosis is evident only a few days after injury, the dissemination has preceded injury. The earliest recognition of miliary tuberculosis due to injury has been ten days. As a rule, it is difficult to maintain that trauma one or more years before played a part in causing miliary tuberculosis. It is highly important that hemorrhage in and about the injured tuberculous lesion be found at postmortem examinations and that the place be located where bacilli entered the blood stream and it should be decided whether that invasion would have occurred if an injury had not taken place. Miliary tuberculosis is frequently a sequence of influenza and measles, as is well known. That a profound blood poisoning which may be due to injury and infection with such bacteria as streptococci may also have generalized tuberculosis as its sequence is not commonly known to physicians. A general shaking up of the entire body or strains during which good muscular coordination is absent are more likely than are crushing injuries to cause tears of imperfectly organized vascular and edematous granulation tissue and result in an infection of the blood stream at that place with large numbers of tubercle bacilli, or to release the organisms so that intimal tubercles elsewhere are formed and serve as depots from which bacilli are discharged into the blood stream. The later is much more common, but at the place injured intimal tubercles in veins may develop or invasion of blood vessels by apposition-necrosis may result.

E R LE COUNT

INTRACRANIAL LESIONS OR ASPHYXIA IN THE NEW-BORN H. HEIDLER, *Ztschr f Geburtsh u Gynak* **91** 235, 1927

This long review is almost wholly based on postmortem examinations, without, however, much reference to microscopic studies. There were six new-born infants who died from contusion of the brain, five from intracerebral, and five from intraventricular, hemorrhage. Hemorrhage into the leptomeninges was responsible for the death of twenty, and of these five were born dead. The most frequent change was a torn tentorium cerebelli, with bleeding under it from lacerated dural sinuses. Of the 131 infants, there was breech presentation in 65, forceps delivery in 37, spontaneous birth in 28 and, strangely enough, cesarean section in 1.

Death from asphyxia alone was relatively uncommon. Evidently, as a consequence of careful postmortem examinations, asphyxia as a cause of death of the new-born infant will be of less importance than it has been heretofore. The examination of the cranium and its content is most important. E. R. LE COUNT

THE RELATION BETWEEN INJURY AND TUBERCULOSIS OF THE TESTIS AND EPIDIDYMIS F. ZOLLINGER, *Ztschr f Tuberk* **48** 119, 1927

It is likely that most of the statements in medical literature about the frequency with which tuberculosis of the testes and epididymis is caused by injury are without proper foundation. For example, in a report of the health of the Prussian army, from 1900 to 1905, of 112 cases, 73 were attributed to injury, in another report by Peter, 22 of 117. Zollinger believes that such ratios are altogether too high. Of 85,623 accidents dealt with officially in the cantons of Aargau and Solothurn in Switzerland, where he is engaged in compensation work for insurance companies, only 157 reports dealt with the question of tuberculosis, and in only three of these was tuberculosis of the testicle and epididymis mentioned. In these, inquiry failed to substantiate the alleged relation to trauma.

Details of these three, of eight hitherto unreported cases and of five from the literature are reviewed. In order satisfactorily to predicate a causal relationship to injury, the circumstances of the injury should be undeniable and there should be symptoms such as swelling of the testicle, subcutaneous hemorrhage and pain. The frequent accounts of "strain" are unimportant, and the tuberculosis does not follow open wounds. Failure of the person to stop working at the time of injury is a good indication that the alleged trauma is without significance. Indirect violence, such as falling and lighting on the feet, which may result in a concussion of the testis or epididymis, is important, but with this exception the violence must occur directly to the parts. The injury must be sufficient to promote localization of bacilli at the wounded place or to loosen tubercle bacilli already mobilized there.

In the last event the tuberculosis antedates the injury, and symptoms of an aggravated active tuberculosis soon begin. When as a consequence of injury bacilli locate in previously healthy epididymis or testicles, the disease should not begin until three or four weeks and not later than from two to three months following the injury. When the consequences of injury merge gradually into outspoken tuberculosis of these parts with such proper time relations and without an interval of entire freedom from symptoms, trauma is relevant. In the spontaneous development without trauma of tuberculosis of these male organs, the disease usually spreads from the prostate gland to the epididymis, and from there to the testis. Prostatic tuberculosis is usually (70 per cent) a sequence of pulmonary lesions.

E. R. LE COUNT

NEPHROLITHIASIS AFTER FRACTURED SPINE E. SIMON, *Ztschr f Urol* **21** 444, 1927

One third of the total amount possible was decided as proper indemnification in the Free State of Danzig for the loss of a kidney removed for stones due to an injury. This was to be paid for three years, because by that time the other kidney would function normally. The injury was fracture of the spine in the lumbar region with paralysis of the lower extremities, which disappeared about four weeks after laminectomy.



About four months after the injury there were symptoms of pyelitis of the right side, and one month later, a diagnosis of stone was made. The kidney was removed six months after the injury, the patient recovered. Blood was found in the urine soon after the fall. The upper pole of the kidney removed had a healed injury in it with blood from an old hemorrhage. The stones were not of the kind, heavily phosphates, which result from inflammation, and the upper pole of the right kidney where the injury occurred was at the level of the transverse processes of the first lumbar vertebra, which were fractured. These were reasons for the decision that the nephrolithiasis was caused by the injury.

Calcium carbonate with a little phosphate was found in one concretion examined chemically. A trace of blood was also demonstrable. Other stones in the kidney resulting from injury have been largely oxalates. Whether or not calcium from the several broken vertebrae and from bones of the lower extremities, which were paralyzed for several weeks, contributed to the formation of stones is also discussed.

E R LE COUNT

#### INJURY OF THE RECTUM AND URINARY BLADDER BY RADIUM AND X-RAYS L. ZEISS, *Ztschr f Urol* **21** 626, 1927

There are repeated observations of ulcers, gangrene and fistulous passages of the urinary bladder and rectum from the use of radium and roentgen-rays which kill remaining tumor cells and prevent recurrences after operations for cancer of the adjacent organs. In women these have followed cancer of the uterine cervix especially, in men, cancer of both prostate and bladder. These irradiation lesions are particularly interesting because they have repeatedly been taken for recurrent tumors. After he had found such masses in the bladder, one surgeon planted the ureters in the front wall of the abdomen, later, when he was ready to remove the entire bladder, he found the tumor absent and the bladder lining smooth and healthy. The lesions are frequently raised, thick, solid masses with broad bases and surfaces beset with warty elevations. The surfaces may be ulcerated and are often heavily coated with urinary concretions. They are high up in the bladder as a rule, and may be as much as 3 or 4 cm in diameter. About the masses, the mucosa is usually edematous, and bullae may be present.

The calculous masses change position and obstruct the urethra, so that it is necessary to crush them repeatedly and remove them in fragments. Tissue removed from these supposed tumors by curetting has been found to be composed solely of an inflammatory exudate and thrombosed blood vessels, both necrotic in places. They are extremely chronic and heal very slowly.

In the three patients with such localized lesions in the bladder reported by Zeiss, all were first noticed months after the radiation and all were at first regarded as recurrences of tumors. Some ulceration was still present in one patient four years after the radium was used. In this patient, a circular stenosis of the rectum also resulted from the treatment, it was firm and fixed, and was first diagnosed as recurrent carcinoma, but it disappeared spontaneously.

E R LE COUNT

### Technical

#### THE VOLUME OF THE BLOOD D C DARROW and T E BUCKMAN, *Am J Dis Child* **36** 78, 1928

A rapid electrometric method for determining the freezing point of small quantities of fluid is described.

AUTHORS' SUMMARY

#### THE CEREBROSPINAL FLUID OF PREMATURE INFANTS J GLASER, *Am J Dis Child* **36** 195, 1928

The most frequent cause of unsuccessful lumbar punctures in premature infants is the pushing forward of the loosely attached dura of the posterior wall of the spinal canal by the entering needle. Unsuccessful lumbar punctures in premature

infants will occur much less frequently if the tap is made with the child sitting in an upright position and when a fine hypodermic needle is used. If the proper technic is used, lumbar puncture in these infants is a relatively safe procedure and is often of great value in the diagnosis of and the treatment for cerebral hemorrhage. Bloody spinal fluid obtained from these infants is suggestive but not diagnostic of intracranial hemorrhage. Blood due to the trauma of the puncture frequently cannot be differentiated from blood present as the result of intracranial hemorrhage. The presence of red blood cells in microscopic numbers in the spinal fluid of premature infants during the early days of life is a physiologic phenomenon. The most common form of intracranial hemorrhage in premature infants is subpial hemorrhage. Fatal cerebral hemorrhages may occur in premature infants without the appearance of gross blood or even an exceptional number of microscopic red blood cells in the spinal fluid. Xanthochromia is a physiologic phenomenon in premature infants during at least the first four weeks of life. The degree of xanthochromia of the cerebrospinal fluid may be conveniently measured quantitatively by means of the icteric index. The icteric index of the cerebrospinal fluid of premature infants is highest during the second week of life. More than half of the yellow spinal fluids of infants give a positive indirect van den Bergh reaction. Yellow spinal fluids occur with a relatively high icterus index, and give neither a positive benzidine test nor a positive van den Bergh reaction. The color of these fluids is presumably due neither to hemoglobin nor to bilirubin but probably to a pigment or pigments intermediate in composition between these two. A positive direct van den Bergh reaction of the spinal fluid is strongly suggestive that the patient has had an intracranial hemorrhage. It may, however, occur in kernicterus without cerebral hemorrhage. Cerebral hemorrhage probably contributes to the degree of icterus neonatorum, and unrecognized cerebral hemorrhage is perhaps the cause of some cases of so-called "physiologic" icterus neonatorum.

H E LANDT

A MODIFIED HALDANE GAS-ANALYZER FOR USE WITH SMALL VOLUMES OF GAS H C BAZETT, *Am J Physiol* **86** 556, 1928

A modified gas analyzer is described which is capable of analyzing mixtures of carbon dioxide and oxygen with a neutral gas in any proportion, in volumes up to 2 cc. The error varies from 0.04 to 0.2 per cent according to the volume of gas available.

H E EGGERS

THE SPINAL FLUID TEST OF TAKATA AND ARA B L MONIAS, *J Lab & Clin Med* **14** 67, 1928

The Takata-Ara test is based on the formation of colloidal mercuric oxide when mercuric chloride and sodium carbonate or sodium hydroxide are added to normal spinal fluid. Fuchsin serves as an indicator and stains the fluid a bluish violet. Pathologic spinal fluids either produce a precipitation of the mercury with absorption of the dye or a change of the color to purple or pink. The flocculation is characteristic of syphilis, while the change of the color is observed in bacterial meningitis. The test has given satisfactory results in more than 100 spinal fluids and compares favorably with the colloidal gold test. In tabes dorsalis, the test is less sensitive than the colloidal gold test. The following solutions are required:

A 0.3 per cent solution of sodium chloride

A 10 per cent solution of sodium carbonate. This solution is recommended by Takata and Ara but can be replaced by a tenth normal sodium hydroxide solution of which the double amount is taken. In cases of meningitis, the change in color is more distinct with the sodium hydroxide than with the carbonate.

A 0.5 per cent solution of mercuric chloride

A 0.02 per cent solution of diamond fuchsin in distilled water

The spinal fluid must be free from blood and should not be kept longer than twenty-four hours before making the test.

A series of ten standard Wassermann test tubes are set up, and 1 cc of the 0.3 per cent sodium chloride solution is placed in the second tube and up to the tenth tube. One cubic centimeter of the spinal fluid is placed in the first and second tubes and after mixing, 1 cc is withdrawn from the second tube and filled in the third tube, this procedure is repeated with the following eight tubes. The last cubic centimeter of the dilution is discarded. There is now a range in the dilution from the concentrated spinal fluid in the first tube to 1:512 in the last tube. One drop from a capillary pipet of the sodium carbonate or two drops of the sodium hydroxide solution are added to each tube and mixed well. The test is completed by the addition of the Takata-Ara reagent. This reagent consists of equal parts of the mercuric chloride and fuchsin solutions mixed immediately before using. The solutions of mercuric chloride and fuchsin keep indefinitely. Three-tenths cubic centimeter is used in each tube. The test tubes are shaken thoroughly and kept at room temperature. Takata and Ara first recommended three readings, namely, after fifteen minutes, thirty minutes and twenty-four hours. Monas believes that some information can be obtained after thirty minutes and that the result becomes final after twenty-four hours. As stated, two different forms of reactions may take place with pathologic spinal fluids.

S A LEVINSON

FURTHER OBSERVATIONS ON THE UROBILINOGEN TEST FOR LIVER FUNCTION  
G B WALLACE and J S DIAMOND, Contributions to Med Science Dedicated  
to A S Warthin, George Wahr, Publisher, Ann Arbor, Mich, 1927,  
pp 407-413

In a large number of normal persons and patients suffering from disease in which the liver was not involved, Wallace and Diamond found the concentration of urobilinogen in the urine to be remarkably constant. In the normal person the urobilinogen content of the urine is below that amount which gives a positive color reaction with Ehrlich's benzaldehyde reagent when the urine is diluted 25 times or more. The age, the time and quality of the food intake, constipation, excretion of indican and the time of collection of the specimen do not influence the reaction.

Wallace and Diamond have produced experimental damage to the liver parenchyma and have induced a measurable increase in excretion of urobilinogen. Parenchymatous disease of the liver, as seen clinically, was accompanied by a similar increase. The main factor in the production of excessive urobilinogen may be an abnormally large formation of urobilinogen in the intestine, but probably in every instance high urobilinogen excretion is an evidence of abnormal function of the liver.

WALTER M SIMPSON

A NEW GOLD SOL FOR THE LANGE TEST FRANK SCOTT LOWWEATHER, Brit J  
Exper Path 9 161, 1928

A modification of the Mellanby and Davies method of procedure for the colloidal gold test is described, in which a double bromide salt is used instead of gold chloride. By this method, more uniform results are obtained.

PEARL ZIEK

A NEW METHOD FOR THE PREPARATION OF BACTERIOLOGICAL CULTURE MEDIA  
CONTAINING AGAR A R GRACE, Australian J Exper Biol & M S 4  
269, 1927

Two pieces of fine gauze are cut about 1 foot square. From a roll of cotton-wool a piece about 8 or 9 inches square and a few millimeters thick is carefully removed, taking care that there are no thin patches, and is laid between the pieces of gauze. The center is then pushed down into a liter Erlenmeyer flask, and the required amount of agar, in a granular condition, is introduced. The pad is then formed into a bag, with the agar in the center, and tied firmly with string at the mouth. The excess gauze is cut off and the bag suspended in the flask by means of strings which are conveniently held by a rubber band around the neck of the flask.

Seven hundred and fifty cubic centimeters of distilled water is poured into the flask and the bag is allowed to float loosely in the water. It is then autoclaved for twenty-five minutes at 120 C, allowed to cool to 100 C, and removed from the autoclave. The bag is raised up toward the neck of the flask clear of the liquid and replaced in the autoclave for ten minutes at 110 C to allow all the agar to drain from the bag. When cool, the empty bag is removed from the flask, leaving the clear agar jelly. The reaction may then be adjusted and the nutrient broth, filtered and adjusted to the same reaction, added.

T BRAILSFORD ROBERTSON

EXAMINATION OF THE CELLULAR CONSTITUENTS OF THE SPINAL FLUID E  
FORSTER, Munchen med Wchnschr **75** 1877, 1928

After centrifugation, the sediment is mixed with a small drop of serum and the mixture divided into three portions on separate slides. The first portion is spread widely and dried in the incubator, the second is spread thin like a drop of blood, and the third is mixed with methyl-green pyronin and examined under a cover glass. After drying and methyl-alcohol fixation, the first and second preparations are also stained with methyl-green pyronin.

EDWIN F HIRSCH

# Society Transactions

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## THE PHILADELPHIA PATHOLOGICAL SOCIETY

*Stated Meeting, Oct 11, 1928*

J HAROLD AUSTIN, *Presiding*

### CARCINOMA OF ABERRANT THYROID (CARD SPECIMEN) E L ELIASON

W M, aged 20, in 1921 was operated on for incision and drainage of a cervical abscess. The microscopic report on the node removed was tuberculosis and, by a second pathologist, normal tissue. In 1927, three nodes were removed from the same site and, after much discussion, diagnosed as carcinoma of an aberrant thyroid. In 1928, another node was removed and regarded as benign adenoma by some and as adenocarcinoma by others.

The section of the node excised in 1921 showed a practically normal cervical node, without evidence of tuberculosis or of the tumor which formed subsequently at the same site.

The node excised in 1927 showed a rather thick fibrous capsule from which thin strands projected into the interior to form the framework of branching papillae. These were covered with a layer of columnar cells. A few of these cells showed mitotic figures. In several places there were small pink-staining masses which might be either colloid or serum, probably the latter. Scattered through the section were deposits of calcium. The diagnosis was papillary cystadenoma of unknown origin, either thyroid or parotid.

The node removed in 1928 showed a preponderance of epithelial cells and little interstitial tissue. Many blood vessels were seen in the supporting framework. In places the cells were in papillary formation, while in others they were in definite acinar formation containing colloid. In most areas the cells were of the low columnar type in single layers, resting on fibrous tissue. There was variation in the size and formation of the acini. In a few areas, the cellular arrangement was indefinite and incomplete. Some of the acini showed an intra-acinar papillary proliferation of the epithelial cells like that seen in hyperplastic toxic goiter. On account of the location of the tissue, the acinar formation with colloid and the immature cells in areas, it seemed that this was an aberrant thyroid undergoing malignant changes.

### SARCOMA OF AN INTRA-ABDOMINAL UNDESCENDED TESTICLE MOSLS BEHREND

J F, aged 29, complained of a swelling in the right iliac fossa. In March, 1927, he consulted a physician, who told him he had an undescended testis and a growth in the abdomen. The swelling did not disturb him until a year later, at which time he consulted another physician who advised operation. The patient said that the mass was getting larger and painful. Operation in March, 1928, revealed a large tumor attached to the cord and lying free in the abdominal cavity. The inguinal canal was not disturbed. The mass measured 14 by 10 by 6.5 cm. One surface was white and smooth, others appeared fleshy and partially lobulated. Section of the tissue showed the entire absence of normal glandular structure, and in its place was a mass of round cells with deeply staining nuclei. A moderate fibrous stroma was present. The diagnosis was small round cell sarcoma.

### MUCOCELE OF THE APPENDIX (CARD SPECIMEN) E L ELIASON

A C, a man, aged 50, complained of pains in the back. These were found to be due to hypertrophic arthritis (x-rays). During the examination, a large mass was found in the abdomen. The patient was not aware of its existence. It was the size of an orange and of the "phantom tumor" type in that it could be made to disappear, reappearing later at a different site. There were no suggestive

abdominal symptoms The specimen presented was a mucocoele of the appendix The microscopic section showed the fibrous coat of the appendix greatly hypertrophied Between the layers of this were areas of lymphocytic infiltration and calcium deposits All that remained of the epithelial lining of the appendix were the few cells which were seen in the lumen

#### AMEBIC COLITIS REPORT OF TWO CASES GEORGE M ROBSON

Because the author believes that the occurrence of a severe and rapidly fatal type of amebic colitis in this part of the country is of interest, he reported two cases The first patient was from Philadelphia, the second from Delaware Unfortunately, no fuller record of their residences and travels is available

The first case was that of a white man, aged 46 years During the summer of 1927, following some dietary indiscretion, he developed diarrhea which continued intermittently for several months This subsided during the fall only to reoccur late in December He was admitted to the service of Dr Stengel at the University Hospital in February At that time he was running a septic temperature and was weak, pale and emaciated He became progressively worse and died in March with evidence of a generalized peritonitis During his stay in the hospital, he had had several severe hemorrhages from the bowels

The autopsy revealed a generalized acute seropurulent peritonitis The small intestines were free from lesions, but the whole mucous surface of the colon was covered by numerous ulcers, varying from a few millimeters to several centimeters in diameter These were acute with soft purulent bases and reddened hemorrhagic margins In most places the entire wall was thickened, soft and inflamed Many of the ulcers penetrated deeply into the muscular layers Just proximal to the splenic flexure there was a large gangrenous area involving almost the entire circumference and measuring 6 cm in length Here the intestinal wall had sloughed away, its contents failing to escape into the general peritoneal cavity only because of adhesions to the omentum and transverse mesocolon The main perforation was on the posterior surface and here the necrotizing process had involved a portion of the pancreas and come almost into direct contact with the portal vein This vessel was thrombosed at this point and from there into the liver it was filled with pus The liver was riddled with pyelephlebitic abscesses

Microscopic examination showed suppurative and necrotizing ulcerations of the colon with many amebas in the lesions Amebas were present deep in the muscular layers of the intestine The liver showed only a suppurative process, no amebas being found in it Cultures and smears from the peritoneal exudate, pus from the portal vein and from the abscesses of the liver showed streptococci and colon bacilli

The second patient, a white man, aged 51, was admitted to the service of Dr Frazier at the University Hospital in April, 1928, complaining of paralysis of the right hand A syphilitic lesion was suspected, and the patient received some mercurial preparation Following this, on May 1, diarrhea and fever developed, which were at first regarded as being caused by the mercury He became progressively worse, with a septic fever and abdominal distention, finally fecal vomiting occurred and a silent abdomen He died in June

At autopsy an acute generalized peritonitis was found The colon including the rectum was the site of innumerable ulcers varying from a few millimeters to a few centimeters in diameter This process was limited to the large intestine, the small intestine being free from ulcerations Some of the ulcers were superficial, but many were deep, eroding and undermining ones Their margins and bases were soft and covered by a purulent exudate In the cecum and sigmoid the process was especially marked with large interstitial abscesses, and a thickened, friable wall In these regions the serosa was covered by a plastic exudate One large branch of the portal vein within the liver was filled by a septic thrombus, but the process was still confined to the vessel and its wall The portion of the liver supplied by this vessel was sharply demarcated from the rest of the liver by its dark red color which contrasted sharply with the lighter yellowish-red of the rest of the organ

Sections from the colon showed a suppurative and necrotizing process with great numbers of amebas in all layers of the wall. Amebas were also seen in several small blood vessels, none were found in the liver. The cerebral lesion was found to be due to a thrombotic process. Bacteriologic examination showed a mixture of streptococci and colon bacilli in the peritoneal exudate, in the pus from the interstitial abscesses and in the material from the portal vein.

The cases are similar in the excessively extensive and acutely ulcerative colitis, and in the presence of a bacterial peritonitis and pylephlebitis. The acute and suppurative character of the lesions of the intestines suggest that bacterial invaders were responsible for at least part of the damage there. It seems evident, from the lack of amebas and the presence of bacteria in the lesions of the peritoneum, portal vein and liver, that these lesions were secondary to the bacterial infection of the amebic ulcers. One is tempted to surmise that the sequence of events in these two cases may have been as follows. There was in each case a quiescent amebic infestation which was rather suddenly incited to acuteness, in one case by diet and in the other by medication, in this way opening a portal for the entry of bacteria which thus gained access to the peritoneum and portal vein and caused peritonitis, pylephlebitis and abscesses of the liver.

#### LEUKOSARCOMA WITH A PRIMARY RETROPERITONEAL TUMOR AND TERMINAL BLOOD INVOLVEMENT D. H. FLASHMAN and S. S. LEOPOLD

A white man, aged 60, gave a history of a swelling in the right inguinal region for twelve months. Biopsy showed lymphosarcoma. A roentgenogram revealed a tumor in the pelvis. The leukocyte count was normal. He was given roentgen treatment for from four to five months, during which time several examinations of the blood gave negative results. In the following month he developed leukemia, the white blood count rapidly increasing to 444,000 cells per cubic millimeter at the time of death. The differential blood count showed from 90 to 96 per cent small lymphocytes. The autopsy revealed a primary, invasive lymphosarcoma in the inguinal and retroperitoneal regions, an extensive involvement resembling leukemia of most of the lymphoid system, liver, spleen and bone marrow of the right femur, and metastatic nodules in most of the organs. In the tissues there were both large and small lymphoid cells, with intermediate types and in various combinations, indicating that these cells represent different degrees of hyperplasia or differentiation. The picture appeared intermediate in character between typical lymphosarcoma and lymphatic leukemia, rather than a combination of two separate entities. The case falls in the group of leukosarcoma.

#### THE RELATION OF VITAMIN B TO INFECTION AND IMMUNITY WITH SPECIAL REFERENCE TO *B. WELCHII* WILLIAM B. ROSE

During the course of an investigation in which dogs were fed a diet deficient with respect to vitamin B, one animal developed severe convulsions. As is well known, such neuromuscular manifestations are typical of vitamin B deficiency. In this particular case, death seemed imminent. The only chance to save the animal's life was the immediate parenteral injection of a vitamin B concentrate (Cowgill, George R. *Am J Physiol* **66** 164, 1923). Accordingly, vitamin powder (Harris) was dissolved, neutralized and sterilized by boiling for three minutes, and the solution was injected subcutaneously. Practically all the symptoms were alleviated within a few hours.

A few days later, however, a mass developed at the site of the injection. Palpation revealed gas crepitus. It was then recalled that the material injected had not been sterilized sufficiently to destroy resistant spores. A provisional diagnosis of "gas infection" was therefore made. The abscess was incised and drained and a pure culture of *Bacillus welchii* isolated. The animal was fed large doses of material rich in vitamin B and recovered rapidly. Repeated cultures subsequently made from the site of the wound proved to be negative for *B. welchii*.

Immunologists agree that dogs are naturally immune to *B. welchii*. However, this dog suffered from vitamin B deficiency when infection occurred, and recovered

rapidly when this vitamin was administered. These considerations suggested the possibility that this vitamin may play a rôle in the maintenance of natural immunity to this organism in dogs.

It should be stated that the diet employed in these experiments was composed of an artificial mixture of isolated food substances. Consequently, it was deemed advisable to determine whether or not dogs possess a natural immunity to *B welchii* under these conditions of experimentation. Accordingly, a series of dogs fed an artificial diet which was complete in every known respect were inoculated with *B welchii*. No untoward symptoms were observed. The same dogs were then deprived of vitamin B, and positive blood cultures were obtained. Vitamin B therapy was then instituted, and the blood cultures became negative. This procedure was repeated a number of times, and the same results were obtained.

These observations suggest that a lack of vitamin B in the diet of dogs lowers their resistance to infection with *B welchii*. However, in view of the fact that dogs suffering from "acute" vitamin B deficiency manifest anorexia, loss in weight and in the advanced stages neuromuscular disturbances, it is obviously unsafe to conclude that the increased susceptibility to infection was due to a lack of vitamin B per se. It was therefore deemed essential to rule out these factors before any precise interpretation could be placed on the results.

Accordingly, dogs were given just sufficient vitamin B to maintain a perfect appetite for the artificial ration. In some instances, there was an actual gain in body weight, the animals remained active and apparently normal. Furthermore, to eliminate the possible effect of confinement on their resistance to infection, they were permitted to run about in an open courtyard and bask in the sunshine. In spite of these favorable conditions of experimentation, positive blood cultures were obtained. The bacteremia was not accompanied by fever or other symptoms. After the administration of vitamin B therapy, the blood cultures were invariably negative. It would appear, therefore, that a state of chronic vitamin B deficiency favors the growth of *B welchii* in the blood stream of dogs.

Another aspect of this subject was investigated. Five dogs, apparently normal, were inoculated with *B welchii*. Massive injections were made subcutaneously, intraperitoneally and directly into the circulation. Blood cultures remained negative for months.

The possibility of a latent infection was considered. After five months these dogs were deprived of vitamin B. In two of these dogs the blood cultures were still negative. These animals finally developed convulsions and died from vitamin B deficiency, postmortem cultures of the internal organs were negative.

Three animals lived and yielded positive blood cultures which became negative when vitamin B therapy was instituted. Hence, it would appear that natural immunity is not a constant phenomenon in this species. Whether or not this variability in natural immunity is directly related to the vitamin reserve of these animals remains to be investigated. The fundamental factors which control the immunity of dogs to this bacterial organism is not clear. It seems, however, that a lack of vitamin B breaks down this natural immunity.

In general, the results appear to indicate that nutritional factors deserve consideration in immunologic studies and that vitamin B in particular merits attention.

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## NEW YORK PATHOLOGICAL SOCIETY

*Regular Meeting, Oct 11, 1928*

HARRISON S. MARTLAND, *Presiding*

### THE DETAILED DIFFERENTIATION OF BACTERIA BY MEANS OF THE MIXTURE OF ACID AND BASIC DYE AT DIFFERENT $p_H$ . A. V. TOLSTOUHOV

As was reported previously, methylene blue-eosin Y mixture can be used for differential staining of bacteria. It gives a fairly deep-staining of bacteria at  $p_H$  about 3 and above. Below  $p_H$  3 the eosin Y stains the bacteria only a pale



pink At this low  $p_H$  the eosin Y is present mostly as an undissociated eosmic acid, and for this reason there is not enough eosin ions to stain bacteria To improve it eosin was replaced by a stronger acid dye—acid fuchsin The mixture, methylene blue (methylthionine chloride, U S P), medicinal, Merck and acid fuchsin can be used successfully at  $p_H$  as low as 0.8 The method of staining by this new mixture is entirely the same as with the old mixture of methylene blue-eosin Y It is sensitive enough to detect the difference in the iso-electric points (1) of single bacteria from the same pure culture, (2) of different strains of *Bacillus coli* and *Bacillus typhosus* The new mixture can also be used for the study of chemical composition of the different parts of the bacterial body Applying it at a certain  $p_H$  it is possible to stain differentially polar bodies of the typhoid group and *Bacillus diphtheriae* These new mixtures are recommended for the staining of *B. diphtheriae* as a substitute for Neisser's stain It is interesting to note that polar bodies of the colon group consist of more alkaline protein than the body of the bacterium itself, they are stained by acid fuchsin The polar bodies of the bacteria, on the contrary, are composed of more acid protein than the bacterial body, they are stained by methylene blue

As a result of this study, the precipitation of the dyes depends on the degrees of hydrolysis of the formed salt, dye and protein of the tissue or other dye If there is salt, weak base and comparatively strong acid (as for example, nucleoproteins or phosphatides above their iso-electric points), the degree of hydrolysis at the same dilution will be the highest in the case of the salt formed with the weakest acid As is known, the gram-positive bacteria are composed of a stronger acid ampholyte than the gram-negative organisms

Combining these facts, one should expect that basic dyes form almost insoluble salts with gram-positive bacteria, on the contrary, the solubility of the salt formed from basic dye and gram-negative bacteria will be much higher

From this purely chemical standpoint the different bacteriostatic effects of basic dyes on the gram-positive and gram-negative bacteria are explained

#### DISCUSSION

ALFRED PLAUT I am not a chemist, but I want to bring before you practical experience from the histologic laboratory, this experience I am sure you all have had from time to time So much has been said about acid and alkali, and the combining of the acid dye with the alkaline tissue, and vice versa I have had the experience when only one slide of an interesting material had been stained with hematoxylin that without doing anything else but bringing it back into water one could stain the same slide for elastic tissue by the Weigert stain Any one can do this with a slide stained previously with hematoxylin or another dye Paraffin sections which were stained first with pyronin-methyl green and later stained with Pappenheim's panoptic stain gave excellent results, occasionally better ones than with the unstained slide The point I do not see, is how these tissues give the same chemical reaction after having reacted chemically with the first dye Furthermore, when tissue is decalcified, it goes through strong acids, then weak alkalis and then water, or when a piece of tissue has been left on the table and dried out, it is put into antiformin, in which the hard material becomes soft again, and still good results are obtained with the staining How is it that material which has been chemically ill treated in such a way gives the same acid-alkaline reaction as it gave before?

HARRISON MARTLAND Is it possible to stain living or dead bacteria with colloidal solutions or are not most of the stains used ionic in character? I had the impression from Blair Bell's work that he was trying to get lead into the cancer cell in colloidal form It was my experience that such colloidal solutions must change into ionic forms before they could penetrate the cell membrane except in such cells as the phagocytic histiocytes of the reticulo-endothelial system

A V TOLSTOUHOV In reply to Dr Plaut's question, I can say that from the chemical standpoint the different compounds used in histologic technic should be divided into three groups

(1) Chemically moderately active compounds, like picric acid, potassium bichromate, mercuric chloride and formaldehyde, which form stable, practically insoluble salts with tissue protein. For this reason they almost permanently change the iso-electric points of the tissue proteins or, in other words, their staining properties.

(2) Chemically weak compounds like dyes, which form more soluble salts with tissue protein than the compounds of the first group. Besides that, the solubility of these salts depends on the reaction ( $p_H$ ) of surrounding mediums. On account of these properties the dyes cannot permanently change the iso-electric points of tissue protein, in other words, the tissues stained by one dye can be stained by another dye without any effect from the previous stain.

(3) Chemically active compounds, like strong mineral acids or strong alkalis. They form a well-ionized salt with tissue proteins, and they cannot change the iso-electric points of tissue protein. The presence of these compounds in smallest quantities in staining mixtures changes effectively the  $p_H$  of the mixtures. In this instance, the  $p_H$  of a mixture and not the compounds themselves change the staining properties of the tissues. The detailed discussion of this subject can be found in my previous articles, delivered before the society in 1926 and 1927.

In reply to Dr Martland's questions, I can say that the dyes often form colloidal solutions, and still they can penetrate the cell membranes. If one considers the toxic effect of a substance, it is not necessary for the dye to penetrate into the cell. To kill the cell it is only necessary to form precipitate on the cell membrane and make the membrane impermeable for food supply or products of the cell metabolism.

THE IMPORTANCE OF THE VESSELS IN THE ROUND LIGAMENT TO THE HEAD OF THE FEMUR DURING THE PERIOD OF GROWTH AND THEIR POSSIBLE RELATIONSHIP TO PERTHES' DISEASE. A. P. ZEMANSKY, JR., and R. K. LIPPMANN

Despite an extensive literature concerning the vessels in the round ligament, little accord has been reached concerning their importance to the femoral head. Recent studies of the pathology of Perthes' disease have strengthened the plausibility that it is primarily an aseptic subchondral necrosis. The possibility that this disease may be directly due to occlusion of the round ligament vessels is thus deserving of further consideration, and has suggested the following study, namely, an effort to determine more accurately whether these vessels are normally of notable importance to the femoral head, especially during adolescence.

A preliminary series of dissections in rabbits showed that the developmental stage of the capital epiphysis in animals, 2 weeks old, corresponds approximately to that of children, 4 years of age. These dissections further demonstrated that, in these animals, the femoral head unites with the shaft at about the age of 7 weeks (18 years in the human being). With regard to this epiphysis, then, the span of life between the ages of 2 and 7 weeks in these animals corresponds roughly to that between 4 and 18 years in the human being, the age period during which Perthes' disease occurs.

A subsequent series of arterial injections, according to the method of Dr Gross, demonstrated that, during this time, there is an artery which courses through the round ligament and enters the femoral head. This artery, however, becomes smaller in size as the animal grows older and an injection could not be made after the age of 7 weeks—approximately the age at which the epiphysis unites with the shaft.

With these facts in mind, we have sectioned the ligamentum teres on one side in a series of rabbits 2 weeks old, thereby obliterating the circulation through the ligament to the femoral head in order to determine the effect of this procedure on the developing capital nucleus. The rabbits were killed at intervals thereafter, and subjected to examination. As control, a similar operation was performed on the opposite hip of the rabbits, but the ligament was not cut. Changes in the

femoral head did not ensue. Also, three adult animals were operated on in a similar manner, the femoral of these animals were not affected.

The femoral head changes which followed the section of the round ligament in rabbits 2 weeks old may be classified as follows:

1 **Anemia** Anemia of the anterior portion and crest of the nucleus was observed first in the femoral heads of the two rabbits killed on the sixth day. Anemia of this area characterized also all of the subsequent specimens observed.

2 **Signs of Bone Necrosis** Pyknosis and failure of the bone cells to stain in the anemic area were first observed in the nine day specimen. The number of the bone cells thus affected increased in the later specimens up to the 22 day old rabbit in which practically the entire anemic area contained only empty cell lacunae.

3 **Marrow Necrosis** Necrobiosis was observed to occur in the marrow cells of the six day specimens. Failure of the hemogenic elements to stain and incipient marrow fibrosis were first apparent in the nine day specimen. Necrosis of the marrow stroma was first observed in the twenty-two day specimen.

4 **Signs of Cessation of Ossification in This Area** Grossly, the relatively smaller size of the bony nucleus was first apparent in the eighteen day specimen. The thickening of the surrounding cartilage and the increased proportion of unossified cartilage in the bony lamellae of the nucleus could be seen microscopically in the same specimen and in all those subsequently observed. The diminution in number of the osteoblasts was first apparent in the nine day specimen. In the last three specimens, osteoblasts were not identifiable in the affected area.

5 **Gross Deformation of the Femoral Head** Flattening of the weight-bearing area and ridging occurred first in the nine day specimen. The later specimens show in addition, pitting and furrowing of the surface. Microscopically, the cartilage of this area is well stained and intact.

6 **Coxa vara** First apparent in the eighteen day specimen and present in all the subsequent ones.

The fact that these changes were, in all the specimens, accompanied by anemia, and the resemblance of these changes to those of infarction, suggest strongly that they were due to the circulatory interference of the operation. When it is considered that the affected area is, at this age period, directly supplied by the vessels of the ligamentum teres (as our injections have shown), and that the changes fail to appear when the operation is performed after the vessels have closed, there can remain little doubt that the pathologic picture results from obliteration of the round ligament circulation alone.

It may thus be concluded from these experiments that the vessels of the round ligament are essential, at least in rabbits, for the normal development of the femoral head, and that interference to the circulation through the vessels at an early age produces an anemia of the weight-bearing portion of the capital nucleus, which, in turn, causes bone and marrow necrosis with ensuing secondary deforming changes. These changes are strikingly similar to those of real Perthes' disease.

Furthermore, our studies have demonstrated that, as adolescence progresses, the importance of these vessels gradually diminishes until the epiphysis unites with the shaft, at which time, in normal animals, the vessels no longer carry blood into the femur and the nutrition of the crest is derived entirely from below.

#### DISCUSSION

P WILLIAM NATHAN I am not sure whether the gentlemen here are interested in the clinical side of Perthes' disease. We have had few opportunities of examining actual specimens in Perthes' disease in the various stages of its development, the specimens we get are all probably from the later stages of the disease and show late terminal changes. I have seen the slides from Dr. Lippmann's experiments. There is no doubt that necrosis of the growing epiphysis occurs after the ligamentum teres is cut, indicating that the blood supply through the ligamentum teres is important to the growing femoral head. The question of

its relationship to Perthes' disease may be another matter, but I am convinced that cutting the ligamentum teres actually results in a necrosis of the spongiosa, and that these changes are similar to those found in specimens from so-called Perthes' disease. It must be admitted, however, that there are additional phenomena to be found in these specimens, namely, changes indicative of an inflammatory reaction as evidenced by the presence of granulation tissue. It must also be admitted that there are some necrotic changes as the result of what is called aseptic necrosis. I think the aseptic part of it is somewhat of a misnomer, because one sees similar changes as the result of streptococcus or other nonsuppurative infection of the joints. I believe that most authors, when they speak of aseptic necrosis, mean simple bone necrosis unattended by suppuration. Avenhausen believes that the majority of these cases are due to trauma which involves the vascular supply and leads to these changes. I think that Dr. Zemansky's and Dr. Lippmann's work will throw light on the condition of Perthes' disease. The disease is one of the growing period, so that it may well be that some trauma that affects the ligamentum teres leads to occlusion of the vessels, and in consequence the changes demonstrated by Dr. Lippmann this evening.

HARRISON MARTLAND Is coxa vara a prominent feature of Perthes' disease?

P. WILLIAM NATHAN There are various malformations and some resemble coxa vara. In former years coxa vara was considered a disease by itself, and supposed to be due to some softening process. We also find the condition known as slipping epiphysis in adolescent boys and girls, and especially in boys who have some disturbance in growth, generally fat boys with a delayed development of the genital organs, the so-called pituitary type, these children are particularly liable to slipped epiphysis, and according to the x-rays, the process in the bone is somewhat similar to the changes in Perthes' disease. We do have cases in which the epiphysis is displaced, but the majority of cases reported as Perthes' disease show softening of the head and bending, and biopsy specimens show destruction of the subchondral spongiosa without any actual microscopic change in the joint. In some there are changes in the epiphyseal disk which remind one somewhat of the changes seen in rickets, though they are obviously not in any way related to rickets. In these children there seems to be a grave disturbance of these structures, not alone in the head of the femur, but in the other spongy bones, a condition which is now called an epiphysitis. We now see cases in which necrotic areas are found in the tarsus, scaphoids and inflamed epiphyses or tibial tubercle. All these cases occur in children, and they will hinder or interfere with the development of the epiphysis. The subject is still not well understood, and in older children these conditions that appear during the course of development seem to have something to do with imbalance of glandular secretion, because all these cases occur about the age of puberty.

HARRISON MARTLAND I was interested in the occurrence of coxa vara. In cases of occupational poisoning by the ingestion of radioactive luminous paint in the watch dial industry, we found a coxa vara present in one of the fatal cases and in two cases in which the patients are still alive. This was attributed to a radiation osteitis of the head of the femur due to the deposition of fixed deposits of radioactive substances in the bones. The marrow was replaced by a loose, fibroblastic and myxomatous tissue similar to that which has been reported as due to mechanical cutting off of the blood supply. Any softening of the femur in this region, no matter what lesion causes it, is likely to cause a coxa vara due to the added weight of the body.

R. K. LIPPMANN I did not expect to take up the clinical application. At present it is impossible to say whether or not we have reproduced true Perthes' disease. We have shown, however, that there must be a balance which exists in the adolescent femoral head between the vessels which cross through the round ligament and those which supply the head from the side, because if the vessels from the round ligament are cut off, a certain part of the head necroses. At a later date this is not true. This balance which probably exists in the human being as

DAVID PERLA I found a reference to a case of Brinsom in a boy, aged 12, who had an obliterative process in the extremities, brain and coronary vessels of the heart, this was briefly reported in 1915. He was unable to explain them on the basis of syphilis. In addition, some one has told me that Vollhard casually mentions a universal endarteritis obliterans as a cause of hypertension, but I have been unable to verify that reference.

#### BASAL CELL CARCINOMA, ADENOID CYSTIC TYPE THREE CASES WITH GENERALIZED METASTASES JOHN W SPIES

For convenience and clarity, the paper is divided into three parts, and in each a distinction is made between tumors having cutaneous origin and those arising in noncutaneous areas.

1 Resume of the literature. An attempt is made to show the gradual change in point of view. The first reports dealt with a somewhat benign process, later ones demonstrated the local malignant condition of some of these lesions, and even the capacity to metastasize to regional lymph nodes (basal cell carcinomas). Rodent ulcer and adenoid cystic epithelioma were often confused with one another. In tumors arising from noncutaneous areas, a distinction must be made between adenoid cystic basal cell carcinoma and adenocarcinoma.

2 The analysis of cases from the General Memorial Hospital. The need of early and effective treatment is emphasized. Roentgen therapy is the method of choice. When surgery is employed, it should usually be as a secondary adjunct. This conclusion is drawn on account of the comparative radiosensitivity in this group of tumors and the fact that surgical failures are numerous. The mortality in the cutaneous group is low, but it is high in the noncutaneous group. The latter result seems to be explained in the majority of the cases by the advanced stage of the disease (usually due to inadequate treatment), and to the anatomic relations of the palate, nose, accessory nasal sinuses, orbit and cranial cavity. It is from these locations that most of the noncutaneous tumors arise, or into which they extend.

It is the opinion of the author that none of the cases from the Memorial Hospital definitely belong to the cutaneous disease known as adenoid cystic epithelioma (Brooke), which may be characterized by a slow course, familial tendency and multiple tumors (usually nonulcerating and benign). Our cases exhibit adenoid and cystic features, but are more closely related to the usual type of basal cell carcinoma (Krompecher), which may be distinguished by more rapid progress, nonhereditary qualities and single growths (usually broken down and malignant).

A detailed description of the histologic structure is given.

3 Case reports. In this disease an important point to be noted in the loss of life that may occur in those patients in whom the disorder remains uncontrolled over a long period of time. This is definitely shown by three cases with generalized metastases. In these, one was primary in the skin near the right nasolabial fold, one arose from the mucous membrane of the nasal septum, and one originated in the submandibular salivary gland, or the skin adjacent to it.

#### DISCUSSION

JAMES EWING Dr Spies has properly emphasized the considerable clinical importance of the fact which these patients demonstrate, that basal cell carcinoma of this type is not the local and confined disease which we had thought it to be, and not one which can be dealt with by temporizing measures. I myself was closely concerned with two of these cases, and when metastases developed in the lungs and the spine, I was greatly surprised. In fact, in both instances, I felt sure from what I had read and seen of the disease before that no such events could be expected. That error has been corrected in the last edition of my book "Neoplastic Diseases," in which it is stated that this tumor may produce widespread metastases. As for the actual identity of all the tumors, it is not necessary to claim that. The cutaneous group and the glandular group from the histologic

standpoint do not show points of essential difference. It is probable that in both instances the cells of origin have similar tendencies which they show in different degrees in recurrences and local and general metastases. The tumors of the tongue and lung are different looking, but of the same general type, and from twelve to fifteen years later the tumor has not greatly changed. The whole experience has taught a new lesson in the natural history of this group of epidermoid carcinomas. I suppose that the reason why this phase of the natural history of adenoid cystic carcinoma has not been emphasized before lies in the fact that under exclusive surgical treatment the patients died before metastases developed or became obvious, whereas under roentgen therapy the local disease is controlled for many years so that the metastases have time to develop and assert themselves.

#### DEMONSTRATION OF A SERIES OF HEARTS ILLUSTRATING SUDDEN DEATH IN CARDIAC SYPHILIS HARRISON S. MARTLAND

Dr Martland presented a series of hearts illustrating the various phases of cardiac syphilis. They were taken from cases of sudden deaths.

Concerning the anatomic route through which the aorta was infected he favored the mediastinal theory of Klotz. In the secondary stage of syphilis, as the stage of spirochetemia passes away, the various organs attempt to rid themselves of the organisms by way of the lymphatics. The important lymph node groups in the mediastinum, especially those around the bifurcation of the bronchi and trachea, become collecting stations or reservoirs for the storage of drained spirochetes. There, they are exposed to the phagocytic action of the histiocytes of the reticulo-endothelial system. Most authorities have for years agreed that the earliest histologic lesions in syphilis involving the aortic root will be found around the vasa vasorum in the adventitia, where there is a mantle of lymphocytes and histiocytes with an obliterating endarteritis. Numerous *treponema* can often be found in these areas. It is, therefore, reasonable to suppose that the lesion in early aortic syphilis is suggestive of lymphatic extension from the reservoirs in the mediastinal lymph nodes by retrograde lymph flow into the perivascular spaces around the vasa vasorum, and that the obliterating endarteritis and formation of miliary gummas occur afterward in the nature of a defense reaction. To support this supposition there were abundant pathologic and clinical observations calling attention to the surrounding mediastinitis and periaortitis. The mediastinal involvement can often be recognized by roentgenographic examinations. The clinical symptoms in aneurysm, especially the pain, are often relieved by anti-syphilitic treatment causing a melting away of the mediastinitis, while the physical signs of aneurysm, such as size, pulsation and murmurs, may be intensified by the relief from the surrounding tense barriers.

His experience has led him to believe that the main and most important lesion in nearly all cases of cardiac syphilis is a supravulvar sclerotic of the aortic root on which most of the other changes and phases of cardiac syphilis depend. The earliest lesions are microscopic and occur around the vasa vasorum in the adventitia of the root of the aorta in which there is seen a collection of lymphocytes and histiocytes in the perivascular lymph spaces. Stained sections of these areas may show numerous spirochetes which have gained access to this area by a retrograde lymphogenous route from the reservoirs of spirochetes in the peribronchial and mediastinal nodes. Small miliary gummas are formed in the adventitia with characteristic histiocytic giant cells, necrosis, etc. A secondary invasion of the mediums follows, with consequent breaking up of elastic tissue and weakening of the vessel wall.

The lesion has now developed to a stage in which it can be recognized grossly. The earliest patch is often a triangular area situated just distal to the mutual attachment of the aortic cusps, in the so-called commissures. The base of the triangle is usually pointed distally. The first patch is often seen in the commissure nearest the orifice of the left coronary artery. The patches are gray, or slightly yellowish, elevated with sharp edges, smooth on top, or marked by shallow

furrows separating trivial secondary elevations. Later, these patches become more or less confluent, and the process spreads in a horizontal manner around the root of the aorta. In his opinion, the sinuses of Valsalva, contrary to most authorities, frequently escape. The syphilitic sclerosis is often extensive and extends over the entire arch to the great vessels of the neck, and sometimes into the descending aorta. Frequently in the decrescent period of cardiovascular life the syphilitic sclerosis is almost entirely masked by a superimposed arteriosclerotic lesion, and in these cases a correct interpretation was always difficult.

The danger of supravulvular sclerosis is three-fold. In about 60 per cent of the cases the process invaded the aortic cusps by way of the commissures, producing aortic regurgitation. The commissures were widened, the free edges of the cusps thickened, the cusps retracted and wrinkled, and marked hypertrophy and dilatation of the left ventricle ensued. Aortic regurgitation is the most malignant type of cardiac syphilis. Patients rarely survive two years after the original diagnosis is made, and intensive treatment is dangerous and of little use.

In about 30 per cent of the cases the supravulvular sclerosis encroached on the orifices of the coronary arteries and produced a narrowing or atresia. This was more apt to occur when the orifices of these arteries were congenitally high placed above the base line, this occurred in many persons. When the orifices had their origin in the sinuses they frequently escaped. Such a narrowing or atresia might account for sudden death with or without pain, or angina and occasionally coronary occlusion indistinguishable from that produced by arteriosclerosis. Real coronary occlusion in his opinion, however, was almost always due to arteriosclerotic changes in the coronaries and had nothing to do with syphilis. Intensive treatment in these cases was dangerous since a too rapid healing of the process about the coronary orifices resulted in scarring and still further narrowing of the openings. A therapeutic paradox was apt to occur. He had never seen syphilis involve the large branches for any extent and thought that specific endarteritis of the terminal branches had been greatly exaggerated.

In about 10 per cent of the cases, aneurysm of the aorta occurred. In many cases of aneurysm he had observed that the heart was not enlarged and that the syphilitic process had not extended to the aortic valve. The valve was, therefore, competent. He thought that the maintenance of a high diastolic pressure, when aortic regurgitation was not present, was an important factor in the production of aneurysm, as in syphilis uncomplicated by arteriosclerosis or nephritis there was only moderate hypertension (150-155 systolic), hardly enough to produce aneurysmal dilatation in a previously weakened wall. The low diastolic pressure in aortic regurgitation often saved the weakened aortic wall from aneurysm. Aside from early supravulvular sclerosis and barring erosion and rupture into adjacent structures, aneurysm was probably the most benign form of cardiac syphilis, since patients could live with large aneurysms for many years.

Provided that the supravulvular sclerosis did not lead to aortic regurgitation or stenosis of the coronary orifices, or aneurysm, many cases of syphilitic aortitis were benign and were found only at autopsy as historical landmarks, apparently not shortening life.

While he did not deny the existence of various forms of specific myocarditis and was in no position to dispute the careful and painstaking histologic work of Warthin, he was under the impression from both pathologic and clinical experience that the importance of these forms of cardiac syphilis had been greatly exaggerated by some pathologists and by many clinicians. Coronary injury distal to the orifices and a specific myocardial inflammation or pericardial injury in acquired syphilis appeared to him to be of little significance. Aside from rare gummas in the cardiac muscle of appreciable size, he had never seen a specific myocarditis that seriously embarrassed cardiac reserve. Sudden death in cardiac syphilis was almost always due to narrowing of the coronary orifices, to aortic regurgitation or to rupture of an aneurysm.

## Book Reviews

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RENE THLOPHILE HYACINTHE LAENNEC A MEMOIR By GERALD B WEBB, M D, President, Colorado School of Tuberculosis, Colorado Springs, U S Government Delegate to the Laennec Centenary, Paris, December, 1926 Price, \$1 50 Pp 146, with 13 full-page plates New York Paul B Hoeber, Inc, 1928

Laennec's short life should be a great inspiration to the medical student and young physician. He began making independent observations when barely 20 years of age and achieved favorable distinction early. He lectured on pathologic anatomy, wrote reviews and abstracts and took part in medical meetings before he obtained his medical degree. He saw that to know disease one must know the underlying changes, and that this knowledge can be gained only by thorough and orderly clinical and anatomic observations. He tells in his own words how he worked. "When a patient enters the hospital it is the duty of a pupil to collect from him those anamnestic facts which he can give concerning his disease, and to follow their course. On examining the patient myself, I dictate the principal symptoms which I observe—those especially which may serve to establish the diagnosis or indications for treatment. And I confirm my conclusion, unless I may have to change it, by subsequent observations. This dictation, which is made in Latin for reasons easily appreciated [Laennec was an accomplished scholar in the learned languages], is taken down by the pupil in charge of the patient, and at the same time on a separate sheet, which I call the 'diagnostic leaf,' to keep which, in order that it may be shown to me and read whenever required at each visit, is the special duty of another pupil. If a new sign appear, such as might modify the first diagnosis, I have that also added. If a patient die, the account of the autopsy is collected by the pupil in charge of the case. I read this account before all those who have been present at the autopsy, and if any correction is to be made, I make it on the spot, after having consulted with them."

He discovered a new method of observation of universal use in medical practice, and he nearly exhausted the field of investigation by that method, with results of the greatest value. Heretofore, there has not been any easily available complete sketch of Laennec in English. There is a good sketch of him by John Forbes in his translation, which has appeared in several editions, the fourth in 1834, of Laennec's "A Treatise on Diseases of Chest and on Mediate Auscultation." In the French there is an excellent biography of Laennec in two volumes by Alfred Rouxau which ought to be translated into English. Webb's little book is an elaboration of an address in 1926 to commemorate the centenary of the death of Laennec, and is reprinted with additions from *Annals of Medical History*, volume 9, 1927. The book traces in a highly interesting way the brief but eventful life of Laennec (1781-1826) and constitutes the best sketch with illustrations in the English language of one of the greatest of physicians.

LABORATORY DIAGNOSIS AND EXPERIMENTAL METHODS IN TUBERCULOSIS By HENRY STUART WILLIS, The Johns Hopkins University and Hospital. With a Chapter on Tuberculo-Complement Fixation. By J Stanley Woolley, Loomis Sanatorium, New York. Introduction by Allen K Krause, The Johns Hopkins Hospital. Price, \$3 50. Pp 330, with 25 illustrations. Springfield, Ill. Charles C Thomas, 1928.

According to the author's introductory remarks, this book "aims to describe the more important methods of the laboratory diagnosis of tuberculosis and to consider some of the more significant procedures and principles involved in the experimental study of the infection." Both aims are well achieved. Any laboratory



worker, whether apprentice or master in the field, will secure reliable results by following carefully the detailed prescriptions in this book, and it may be ascertained as a fact that what Dr Krause states as a hope in his introduction will "rid a respectable proportion of practitioners of an inferiority complex" in regard to the diagnosis of tuberculosis, by showing them convincingly "that the laboratory diagnosis of the ordinary case of tuberculosis can be accomplished by simple methods in an ordinary physician's hands in an ordinary physician's office" This is accomplished by describing in minute detail every step in the bacteroscopic diagnosis Other laboratory procedures, such as cultural and inoculation methods and serologic and hematologic technic, are mentioned in full with proper emphasis on their purely auxiliary nature There is a discussion on the technic, the importance and—last but not least—the limitation of tuberculin tests in diagnosis, which is of high practical value Experimental methods, such as animal inoculation, including valuable remarks on the anatomy of laboratory animals, and the characteristics of induced tuberculosis, histologic and explanation methods are presented with a clarity which only thorough familiarity with the subject can produce Theoretical knowledge, the minimum necessary for practical work, is imparted in simple and brief discussions A second edition, which should follow this book within a short time, should give an opportunity to the author to correct the rather frequent mistakes in spelling of foreign references The references always include the original articles on each subject, a commendable practice When it comes to the summing up of the experiences up to the present time, however, the reviewer should like to see, in a few instances, some more modern references than the ones quoted But in spite of these two points of criticism, it should be emphasized that Dr Willis' work has set a high standard of practicability and reliability Dr Woolley's chapter on tuberculocomplement fixation is well presented, concise and, though cautious in its conclusions, far from pessimistic A wide distribution of this book would be instrumental in raising the standard of the diagnostic work in tuberculosis

CLINICAL PHYSIOLOGY (A SYMPTOM ANALYSIS) IN RELATION TO MODERN DIAGNOSIS AND TREATMENT A TEXT FOR PRACTITIONERS AND SENIOR STUDENTS OF MEDICINE By ROBERT JOHN STEWART McDOWALL, D Sc, M B, F R C P, Edinburgh, Professor of Physiology, King's College, University of London With an Introduction by W P HALLIBURTON, LL D, F R C P, F R S, Emeritus Professor of Physiology, King's College, University of London Pp 383 New York D Appleton & Company, 1927

This book is a readable summary of the views held by the present school of British physiologists in their interpretation of clinical symptoms It is not a reference book, and clinical syndromes are rarely treated in detail The bibliography contains only reviews by important workers in the various fields The parts dealing with the physiology of muscle and nerve, circulation and the respiratory function of the blood are the best, representing the views of Starling, Barcroft, Hill and others The sections on metabolism, gastro-intestinal physiology, endocrinology and the vitamins are not nearly as good by comparison, and the reader is disappointed not to find reference to many important American contributions in these fields The book should be of distinct value to the clinician who wishes to acquaint himself with modern conceptions in physiology, but the investigator will find little of service in so short and general a treatise

## Books Received

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RENE THEOPHILE HYACINTHE LALNNEC A Memoir By Gerald B Webb, M D, President, Colorado School of Tuberculosis, Colorado Springs, U S Government Delegate to the Laennec Centenary, Paris, December, 1926 Price, \$1 50 Pp 146, with 13 illustrations New York Paul B Hoeber, 1928

FOOD, NUTRITION AND HEALTH By E V McCollum, Ph D, Sc D, and Nina Simmonds, Sc D (Hygiene), Professor and Associate Professor of Chemical Hygiene, School of Hygiene and Public Health, Johns Hopkins University, Baltimore Ed 2, revised Price, \$1 60 Pp 148 Baltimore Published by the authors, East End Post Station, box 25

This book gives a clear, well written and nontechnical account of the newer knowledge of foods and nutrition in relation to health, and it should be given the widest possible distribution

DIE BIOLOGIE DER PERSON Ein Handbuch der allgemeinen und speziellen Konstitutionslehre unter Mitarbeit zahlreicher Fachmanner Von Prof Dr T Brugsch und Prof Dr F H Lewy Volume II Price, 20 marks Pp 269, with 18 illustrations Berlin Urban and Schwarzenberg, 1928

INTERNATIONAL CORN BORER INVESTIGATIONS Scientific Reports 1927-1928 Edited by Tage Ellinger, Sc D Pp 237 Chicago International Live Stock Exposition, Union Stock Yards, 1928

DIE TUBERKULOSE UND IHRE GRENZGEBIETE IN EINZELDARSTELLUNGEN Beihefte zu den Beiträgen zur Klinik der Tuberkulose und spezifischen Tuberkuloseforschung Herausgegeben von L Brauer-Hamburg und H Ulrici-Sommerfeld Volume VI Ausgewählte Schriften zur Tuberkulosepathologie Von K E Ranke Weiland, Professor an der Universität München Herausgegeben und Eingeleitet von W und M Pagel Price, 20 marks Pp 236, with 25 illustrations Berlin Julius Springer, 1928

## THE PHYSIOLOGY OF VITAMINS

### V CUTANEOUS MANIFESTATIONS RELATED TO A DEFICIENCY OF THE VITAMIN B COMPLEX \*

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CHARLES J STUCKY, PH D

AND

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NEW HAVEN, CONN

There is a rather widespread belief that a liberal intake of the vitamin B complex<sup>1</sup> is important in preventing the development of various lesions of the skin. The basis for such a belief is probably to be found in the reports of favorable results in such cases following the administration of yeast. This, coupled with the fact that yeast is a good source of vitamin B, led to the conclusion that vitamin B is the factor responsible for the therapeutic results. Records of observations indicating such a relationship in either human beings or lower animals that were subsisting on rations carefully controlled in content of vitamin B and complicated as little as possible therapeutically by dietary variables are scarce. Hawk and his associates<sup>2</sup> carefully reviewed the literature concerning the therapeutic uses of yeast, and reported their own observations on ninety-one cases. Their numerous tables indicate that yeast may be administered to advantage in cases of furunculosis, acne and constipation. Valuable as these observations are, they do not allow the conclusion that the vitamin B in yeast is responsible for the beneficial effects obtained. The general results reported by Hawk and his associates were subsequently confirmed by Welker and Hentz<sup>3</sup>.

The literature concerning the antineuritic vitamin as studied in different species of animals does not make any point of the cutaneous manifestation of a deficiency of vitamin B. Likewise, the literature on

\* Submitted for publication, Aug 2, 1928

<sup>1</sup> From the Laboratory of Physiological Chemistry, Yale University

1 The substances containing vitamin B used in these experiments contained both the antineuritic and the heat stable components of this vitamin. Therefore, the expression "vitamin B complex" is used. The basal ration was relatively free from both of the B fractions just named.

2 Hawk, P B, Knowles, F C, Rehfuess, M E, and Clark, J A. The Use of Bakers' Yeast in Diseases of the Skin and of the Gastro-Intestinal Tract, J A M A 69 1243 (Oct 12) 1917

3 Welker, W H, and Hentz, E L. Arch Therap 5 152, 1926

beriberi, although mentioning the occasional occurrence of lesions of the skin, does not emphasize them as characteristic elements of the syndrome. It may well be questioned whether the beneficial effects attributed to the administration of yeast are really due to the vitamin B involved. The fact that among the many clinical conditions tested by the therapeutic administration of yeast, only furunculosis, acne and constipation should yield at all readily to such treatment, suggests that the primary cause of the improvement in such cases is to be sought in such factors as change of the intestinal flora, diminution of putrefaction and enhancement of intestinal motility. In other words, yeast may be regarded as achieving results as do most so-called "blood purifiers," namely, by altering and improving conditions in the lower part of the alimentary tract.

More recently, the value of a concentrate of vitamin B in the treatment of pellagra was reported by Goldberger and his associates<sup>4</sup>. It is pertinent to the theme of this paper to mention the fact, well recognized by clinicians, that dermatitis is part of the syndrome characteristic of pellagra. In the studies of Goldberger and his co-workers, it appears that there is evidence that a deficiency of what has been spoken of hitherto as vitamin B may be a factor in the development of certain lesions of the skin.

According to Gerstenberger,<sup>5</sup> vitamin B has an unmistakably curative effect in cases of herpes stomatitis and herpes labialis. Lesions of these conditions in thirteen children and one adult yielded in remarkable fashion to the oral administration of a concentrate of vitamin B. Other dietary variables of the nature of vitamins were ruled out as therapeutic factors by the fact that the curative concentrate contained only the vitamin B complex.

In the course of nutritional experiments carried out by one of us (G. R. C. during 1923-1924) there appeared in dogs subsisting on artificial rations (tables 1 and 2) two well defined cases of ulcers, which were formed particularly on the bony prominences of the lower fore limbs. The fact that the dietary histories of the animals that showed such lesions were known for long periods—from seven months to more than a year—gave to these observations a unique significance. However, the scars of presumably the same lesions were also observed frequently in other dogs of our colony that were not subjects of nutritional experiments. More recently, two of us (C. J. S. and W. B. R.), in three series of experiments, placed groups of dogs on a regimen deficient

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4 Goldberger, J., and Lillie, R. D. U. S. Pub. Health Rep. **41** 1025, 1926.  
Goldberger, J., Wheeler, G. A., Lillie, R. D., and Rogers, L. M. U. S. Pub. Health Reprint no. 1062, p. 297, 1926.

5 Gerstenberger, H. J. The Etiology and Treatment of Herpetic (Aphthous and Aphtho-Ulcerative) Stomatitis and Herpes Labialis, Am. J. Dis. Child **26** 309, (Oct.) 1923.

in vitamin B, with a view to studying the changes in the blood and the gastro-intestinal tract and other changes associated with such a dietary condition, and in the course of these investigations they noticed in certain animals the appearance of similar lesions of the skin

### THE LESIONS

Figures 1 and 2 show early and late stages of the lesions. Through the courtesy of Dr M C Winternitz of the Department of Pathology of the Yale University School of Medicine, who observed the lesions and arranged for their reproduction in colors, we are able to give the following description

The illustrations amply portray the details of the anatomic lesions, in both the early and the late stages. It is obvious that these lesions were usually symmetrically placed, that they involved particularly the bony prominences, on both the flexor and the extensor surfaces of the fore and the hind limbs. The lesions were invariably round or slightly oval. In the early stages, they appeared slightly elevated, pink and denuded of hair. Gradually, the elevated zone was sloughed

TABLE 1—*Casein Diet III*\*

Components	Grams	Calories	Per Cent
Casein, commercial (12.7 per cent nitrogen)	63	20.6†	41.2
Sucrose	45	18.0	29.4
Lard	2.8	25.2	18.3‡
Butter	1.1	9.0†	7.2‡
Bone ash	0.4		2.6
Salt mixture§	0.2		1.3
Total	15.3	72.8	100.0

\* One kilogram of this food contains 0.8 Gm. of nitrogen and 73 calories, 46.5 per cent of which are furnished by fat. A discussion of the kilogram unit may be found in Cowgill J Biol Chem 56:725, 1923.

† Calculated on a basis of 81.9 per cent protein.

‡ Figured as containing 90 per cent fat.

§ The salt mixture was made as follows: sodium chloride, 10 Gm.; calcium lactate, 4 Gm.; magnesium citrate, 4 Gm.; ferric citrate, 1 Gm.; and iodine potassium iodide solution (Lugol's), a few drops.

away, leaving behind a sharply punched-out ulcer, very similar indeed to the gastric ulcer, as it appears in man. Their appearance was as though a sharp instrument had been used in punching out the holes. They differed from the gastric ulcer in that they were not terraced but had precipitous sides. In the course of the formation of the ulcer from the early to the late stage, as is indicated on the hind quarter (right) in figure 2, the center of the elevated zone first sloughed away, and the sloughing gradually extended to the margin of healthy tissue. When the ulceration was completed, the base was brilliant red, smooth and clean, and, as soon as the necrotic material had been eliminated, this clean appearance remained. Accumulations of exudate were not encountered. This may have been due to the constant licking of the sores by the animal.

### REPORT OF CASES

*Fust Group, 1924*—CASE 1—Dog 55, a female mongrel, weighing 7.5 Kg., received casein diet III (table 1) plus 0.6 Gm. per kilogram each day of "Vitavose"¶

¶ Obtained from the Ward Baking Company, New York. Now obtainable from E. R. Squibb & Son, New York.

(a commercial product rich in vitamin B) The animal was in excellent condition and maintained a good appetite, eating all the food offered for 262 days (approximately eight and two-thirds months), which was the length of the period during which the basal diet was supplemented by the source of vitamin B (period 1) The body weight at the end of period 1 was 9.8 Kg During period 2, the daily supplement of "Vitavose" was omitted Complete, voluntary ingestion of all food offered occurred for fifty-seven days From then on, the appetite was capricious, and a lethargy developed associated with conjunctivitis and the appearance of sores on the bony prominences of the limbs The body weight was 8.3 Kg on the ninety-first day On the ninety-second day of this period, the spastic paralysis characteristic of advanced deficiency of vitamin B appeared "Vitavose" was administered by stomach tube repeatedly, but the material was not retained Death resulted Autopsy revealed lobar pneumonia as a complication

CASE 2—Dog 56, a female mongrel of the fox terrier type, weighing 61 Kg, received meat residue diet IV (table 2) plus 0.6 Gm per kilogram per day of "Vitavose," the latter administered separately The animal ate all food offered

TABLE 2—*Meat Residue Diet IV*<sup>\*</sup>

Components	Grams	Calories†	Per Cent
Meat residue ‡ {13 per cent nitrogen {10 per cent fat	6.15	21.6 5.67	37.3
Sucrose	5.63	23.5	34.1
Lard	3.00	28.4	18.2
Butter	1.12	9.46§	6.7
Bone ash	0.4		2.5
Salt mixture#	0.2		1.2
Total	16.50	88.6	100.0

\* One kilogram of this food contains 0.8 Gm of protein nitrogen, 1 Gm contains 5.63 calories

† Loewy's factors are used, namely, 4.32 for protein, 4.18 for carbohydrate and 9.46 for fat

‡ From the Valentine Meat Juice Company, Richmond, Va

§ A 10 per cent correction for the salt and water content

# Salt mixture given in table 1

and remained in an excellent nutritive state for the entire period of 230 days—approximately seven and two-thirds months At the end of period 1, the body weight was 6.8 Kg During period 2, the daily administration of "Vitavose" was omitted Seven days later, the animal showed the first sign of anorexia The dog had a capricious appetite for the next twenty-eight days The animal was then given one large dose of "Vitavose" This was followed by a perfect intake of food for eight days, after which the appetite again became erratic Another single dose of the material containing vitamin B was associated with a restoration of appetite for a period of seven days The dog was then given casein diet III, without the supplementary vitamin, for a period of sixty-three days The appetite was capricious during this time The preulcerative condition portrayed in figure 1 was noticed The dog weighed 6.1 Kg Otherwise, the nutritive condition of the animal appeared satisfactory When the diet was rendered adequate by supplying the missing vitamin separately, the intake of food again became complete, and the preulcerative lesions improved horny dry scablike tissue, presenting the general appearance of a scar, was the only sign of the sores

In the case of dog 56, there was presented, quite apart from the particular theme of this paper, a perfect demonstration of the validity of the hypothesis that a deficiency of vitamin B is associated with certain pathologic conditions For over seven months this animal was maintained in excellent condition, as far as one could judge from appearances, with a perfect voluntary intake of food,

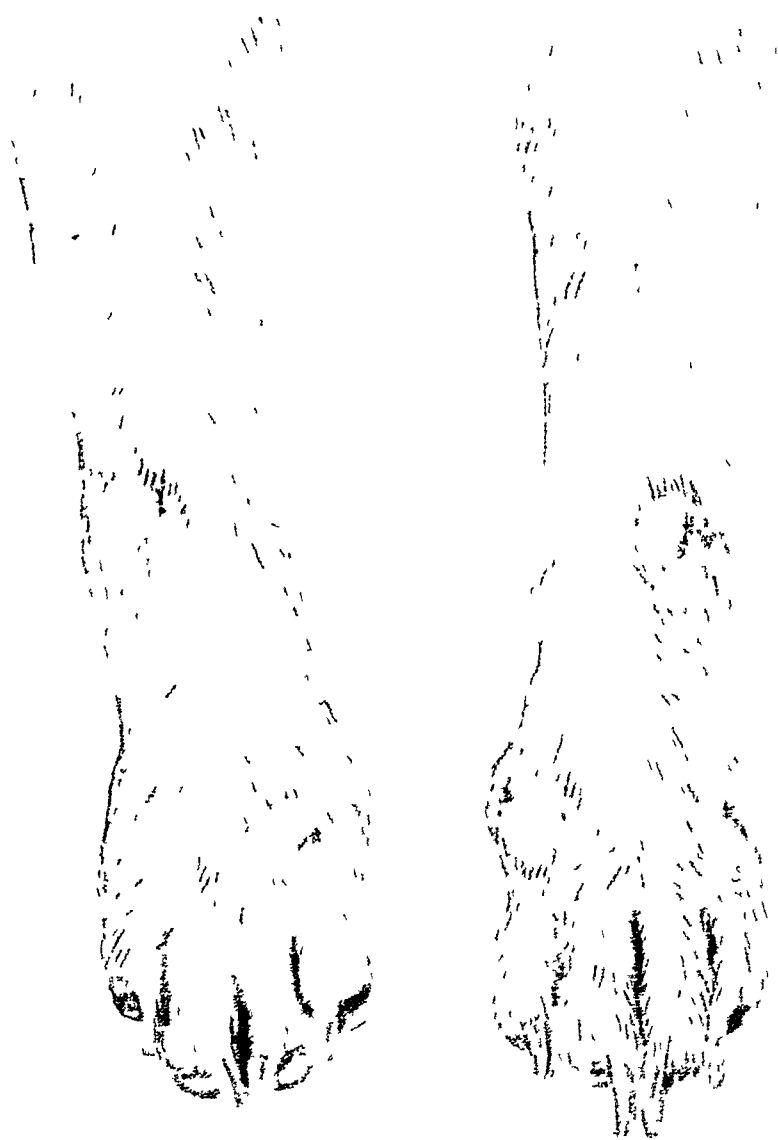


Fig 1—Symmetrically placed lesions on the fore limbs of a dog subsisting on rations deficient in vitamin B The early stage of the sores is depicted







Fig 2—A later stage of the lesions due to deficiency of vitamin B. The center of the elevated zone shown in figure 1, first sloughs away, as shown here on the right hind quarter, and the sloughing gradually extends to the margin of healthy tissue, leaving a smooth, clean brilliant-red base.



on a basal ration free from vitamin B, supplemented by a carefully measured amount of a material containing vitamin B. On merely withholding the supplementary vitamin, making no other change in the dietary conditions, we were able to bring about, after approximately a week, a loss of appetite in the animal, and, conversely, we were able promptly to correct this loss of appetite by a separate administration of a single dose of the material containing the vitamin. A second loss of appetite was corrected in similar fashion.

*Second Group, June, 1926, to August, 1927*—CASE 3—This case occurred in the first series of experiments with casein diet III. Ulcers on the ear of a dog were first noticed on the twenty-first day of the period of deprivation of vitamin B. These ulcers grew worse, and others appeared on different parts of the body, especially the joints and the feet. Local treatment with mercurochrome-220 solution and other applications was little, if at all, effective. A remedy for mange and frequent baths seemed to effect improvement in the condition of the skin only temporarily. Generalized so-called "polyneuritic" symptoms characteristic of advanced cases of a deficiency of vitamin B appeared on the sixty-second day of the deficiency regimen. Therapeutic treatment with vitamin B was instituted, a commercial "yeast vitamin powder (Harris)"<sup>7</sup> being used. The nervous and muscular symptoms soon disappeared. On the eighty-fourth day of the experiment—the twenty-second day after the first administration of vitamin B—the animal was apparently normal. The sores had healed.

CASE 4—Case 4 occurred in the second of three series of experiments with casein diet III. An ulcer on the plantar surface of the forepaw of a dog was first noticed on the thirty-ninth day of the regimen deficient in vitamin B. The animal's general condition grew worse, and more ulcers appeared on other parts of the body. Both forepaws were ulcerated on the forty-fourth day. Obvious changes in the dog's general condition did not appear until the sixty-sixth day, on that day, the animal died, after exhibiting severe symptoms of "polyneuritis." Several doses of material that contained the vitamin were administered by mouth before death, but all were vomited.

CASE 5—Case 5 occurred in the second of the three series of experiments with casein diet III. Ulcers on bony prominences of the limbs of a dog were first noticed on the thirty-sixth day of the regimen deficient in vitamin B. The sores continued and grew somewhat worse. On the sixtieth day, the animal died suddenly with symptoms of advanced deficiency of vitamin B.

CASE 6—This case occurred in the third series of experiments with casein diet III. Ulcers on the limbs of a dog were first noticed on the twenty-eighth day of the deficiency of vitamin B. The sores increased in number and grew worse until, on the forty-first day, they were present on the bony prominences of both fore limbs, the most serious lesions being at the elbow. "Polyneuritic" symptoms appeared on the forty-third day. Vitamin B was administered therapeutically with success. On the sixty-sixth day, the animal still showed a general erythema. The blood sugar level was normal. On the seventy-first day of the experiment—the twenty-eighth day of the treatment with the vitamin—a general erythema somewhat characteristic of mange was still present, but the ulcers on the bony prominences of the limbs had disappeared.

CASE 7—This case occurred in the third series of experiments with casein diet III. One large ulcer on the thigh of a dog was noticed on the sixtieth day of the deficiency of vitamin B. It showed a remarkably clean base, evidence of local infection was absent during its development. It appeared to come suddenly

<sup>7</sup> From the Harris Laboratories, Tuckahoe, N. Y.

as a large exfoliation of a slough. The ulcer was about the size of a fifty cent coin. The edges of the ulcer were not edematous, red or inflamed, hence not apparently infectious in nature. Determinations of the blood sugar revealed normal values throughout. The animal died suddenly on the sixty-seventh day of the deficiency regimen, before therapy with vitamin B was effective. The dog used as a control on the water and the food regimen did not manifest any gross morbid changes in the epidermal structures.

**ADDITIONAL CASES OF INTEREST**—Two animals that had served as the subjects of a research in the Department of Pathology had been fed for a considerable period on a diet of commercial dog biscuit. These dogs, after a time, developed anorexia, became exceedingly thin and showed ulcers of the type described in this paper. Each dog was then given daily several large doses of a yeast vitamin concentrate. One animal failed to show any improvement, its urge to eat could not be restored, with the result that the starvation continued and the animal eventually had to be put to death. The other dog received two of the daily dosages of vitamin before it recovered its desire to eat. The improvement in the condition of the ulcers was obvious before the animal had eaten much food. This result suggested that the curative effect of the preparation administered was attributable to the vitamin contained therein rather than to the general improvement of the nutritive condition associated with the intake of food following a restoration of appetite.

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## COMMENT

Two of our animals developed the sores after approximately a month of subsistence on the diet deficient in vitamin B, and treatment with a concentrated preparation of vitamin B resulted in the healing of the lesions. Animal 3, after a period of rest on an excellent diet, was again placed on the diet deficient in vitamin B, and thirty-nine days later it again exhibited the sores (case 4). This parallelism between the subsistence on diets deficient in vitamin B and the development of the lesions is worthy of emphasis.

In seeking an explanation why these lesions did not appear in all the animals subjected to the experiments, we were impressed with the consideration that the factor of local injury—pressure (?) in these cases—might have been variable, some dogs lying down for a greater part of the time than others.

The absence of gross evidence of local congestion, edema, excessive heat, tenderness and other signs of an inflammatory process in these lesions particularly emphasized the malnutritional rather than the inflammatory character of the lesions.

The reader may ask whether our data enabled us to relate the lesions at all specifically to the heat-labile antineuritic fraction of the vitamin B complex or to the heat-stable growth promoting substance. In answer, we can state only that both of the materials used as sources of vitamin B in these experiments, namely, Harris' "Yeast Vitamine Powder" and "Vitavose," have been shown to be capable of supporting growth in young rats fed on a diet adequate except for what up to the present has been called vitamin B.

These observations may prove of clinical value. As is well known, chronic invalids subsisting on a "hospital" diet are particularly prone to develop decubital ulcers, which are discouragingly resistant to treatment by the usual methods employed. Our observations suggest that more attention should be paid to the content of vitamin B in the diets used in such cases. Concentrates of vitamin B are now available commercially. Such preparations added to the routine diet may possibly prove of therapeutic value, and will probably improve the patient's appetite. In this way, the general nutritive state of the patient may be improved and healing favored.

#### SUMMARY

Lesions of the skin, frequently symmetrical, were observed in six dogs subsisting for long periods on artificial diets adequate except for the vitamin B complex. In two animals, the administration of a preparation rich in vitamin B was followed by a definite healing of these sores without any other treatment. One dog, after approximately a month's subsistence on the deficient diet, developed what appeared to be preulcerative stages of such lesions. The administration of the vitamin corrected the partial anorexia and checked the further development of the potential sores. The remaining three animals died suddenly of deficiency of vitamin B before treatment with the vitamin was effective.

The relation of the individual components of the vitamin B complex to such lesions of the skin remains to be determined.

# THE EFFECT OF CERTAIN TOXIC SUBSTANCES IN BACTERIAL CULTURES ON THE INTESTINAL MOVEMENT

II EFFECT OF FILTRATES OF YOUNG CULTURES OF THE COLON-  
TYPHOID GROUP OF ORGANISMS ON THE INTESTINAL MOVE-  
MENT OF RABBITS AS RECORDED BY A NEW CINEMA-  
TOGRAPHIC METHOD, CORRELATION OF THIS EFFECT  
WITH THE PRODUCTION OF FOOD POISONING  
BY MEMBERS OF THIS GROUP \*

E E ECKER, PH D

AND

M S BISKIND, M A

CLEVELAND

In a previous study, Ecker and Rademaekers<sup>1</sup> showed the effect of filtrates of young broth cultures of *Salmonella aertrycke* on the motility of segments of the small intestines of rabbits in situ in the living animal. It was found that a strong and gradual rise of the diastolic and systolic tone occurred, i e, spasmodic contraction of the intestinal muscle. In their report, it was stated that with Sollmann and Rademaekers' modification of the Baur technic the stimulation of the longitudinal muscle was accompanied by a strong stimulation of the circular muscle and, therefore, also by increased propulsion of the intestinal contents. Broth alone failed to induce the reaction. In that study, only the aertrycke type of bacilli was used. In the work presented in this paper, however, all the most important members of the colon-typhoid group of organisms were employed. Furthermore, the technic was completely revised to avoid the use of urethane for the anesthetic, and large quantities of Locke's solution. Dr Torald Sollmann suggested the use of liquid petrolatum instead of Locke's solution. The newer method also permitted observations of the larger portion of the alimentary tract without its normal position and relationships being disturbed. The intestinal movements were recorded with a 16 mm Bell and Howell motion picture camera. Finally, we attempted to correlate the new observations with the known activity of the group in the production of acute gastro-intestinal disturbance in man and animal.

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\* Submitted for publication, Sept 5, 1928

\* From the Departments of Pathology and Pharmacology, Western Reserve University School of Medicine

1 Ecker, E E, and Rademaekers, H J Exper Med **43** 785, 1926

## METHOD

Nineteen strains of the organisms were employed. The typhoid strains were newly isolated and were used after five transfers. An original aertrycke (de Nobele) was also used. The organisms were grown for from seventeen to twenty-four hours at 37 C, on 2 per cent Witte peptone veal infusion broth with a  $p_H$  of  $\pm 7$ . The cultures were then filtered through a Berkefeld N candle, and a portion of the filtrate was always used immediately thereafter for intravenous injection. The remainder was discarded. Sterile pure broth filtrates were injected for controls in a number of animals, and a reaction was not seen in any case except in one animal which had been on a diet of green vegetables.

Animals that showed the slightest evidence of a gastro-intestinal disturbance were not used. One half of the animals, twenty, were used for controls to determine the toxicity of the filtrates in the whole animal. The other group of twenty animals were etherized and their spinal columns severed by crushing in the lower thoracic region, hemorrhage being avoided. This rendered insensitive practically the entire ventral abdominal wall of the animal. From one to two hours or more

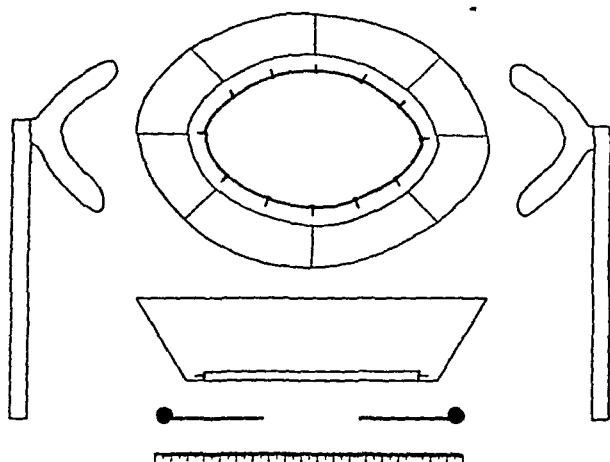


Fig 1—Diagram of the trough and supports used for the observation of the intestines of the rabbit in situ. The scale is in millimeters.

were allowed to elapse following the animal's recovery from the ether before laparotomy was performed.

Laparotomy was done as follows. The hair on the abdomen was clipped closely and petrolatum applied. A median incision about 15 cm in length was made through the skin of the abdomen and the skin dissected free from the underlying muscle. The skin was then hooked back over the ring at the lower rim of a bottomless trough, which, for photographic reasons, was dull black, with dimensions as denoted in figure 1. The trough was then raised on its supports (figs 1 and 2) and the pouch thus formed was filled with liquid petrolatum at 38.5 C. The petrolatum previously applied assisted in making a leak-proof seal around the bottom of the trough and prevented hair from floating into the oil. A second incision was then made through the linea alba, and the muscle and peritoneum were hooked back over the ring. If necessary, sufficient oil was added to cover the intestines in order to avoid confusing reflections from the surfaces exposed to the air. If the cecum or colon, or both, were found distended with gas and floating above the surface of the oil, catheterization was resorted to for emptying the colon, and a hypodermic syringe was used for emptying the cecum, puncture of the

blood vessels being avoided. This was necessary in about one half of the animals. The small intestine was not in any event disturbed.

As a rule, the intestine remained quiescent for from ten to fifteen minutes following laparotomy. Then rhythmic longitudinal muscle movements (pendulum) appeared in the small intestine. Mechanical stimulation was avoided as much as possible. This in the case of the small intestine, was never seen to cause excitation but frequently caused depression for short periods.

Injection of the filtrates was made in the posterior auricular vein.

For lighting and maintaining a constant temperature we used a 15 ampere direct current carbon arc lamp with a single 4 inch (10.16 cm) condensing lens, which rendered the light beam approximately parallel. The beam was reflected from a mirror into the trough (fig 2). This gave sufficient illumination for cinematography and provided just sufficient heat to maintain a constant temperature (38.5 C) in the pouch, in a room where drafts were avoided. By shutting off the arc for short periods or using a 40 candle power carbon filament lamp in front of a

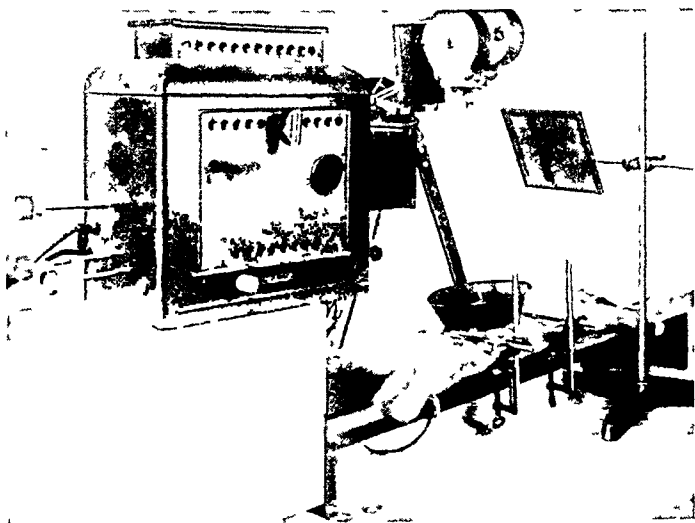


Fig 2—The arrangement of the apparatus for making a moving picture of the intestines of the rabbit in situ. A 15 ampere D C arc is used for illumination. A 6 inch (15.24 cm) square mirror reflects the light into the trough. The camera is supported on a tripod with a tilting top.

reflector, the temperature of the oil in the trough was carefully controlled and was not allowed to vary more than 1 degree, but such procedures were seldom necessary.

The camera was fixed at a distance of about 15 inches (37.54 cm) directly above the trough and centered by the use of a gun-sight. Ordinarily, from one-half hour to one hour was allowed to elapse after laparotomy, then a cinematographic picture of the normal activity of the intestines was taken. This procedure was adopted as routine. Following this, the filtrate was injected in doses varying from 3 to 4 cc. Uninterrupted observations were then carefully made for as long as four hours thereafter. Cinema pictures were taken whenever a definite change occurred. Ordinarily, violent reactions were noted when the filtrate was effective. Some animals were given normal broth about two hours prior to the injection of toxic filtrate, as indicated in table 1. One control rabbit exhibited an incomplete peristaltic rush following the injection of the plain broth.



This occurred in the early spring when fresh vegetables had been given to the animals. Other control animals did not exhibit the phenomenon either normally or following the injection of the plain broth.

Table 1 is a compilation of the results obtained with nineteen strains of organisms.

#### OBSERVATIONS

In these experiments, as stated, seven important subgroups of the colon-typhoid bacilli were studied. Three strains of *Eberithella typhi*, two strains of *Salmonella paratyphi* A, three strains of *S. enteritidis*, two strains of *S. schottmulleri*, four strains of *S. aertrycke*, two strains of *S. supestifer* and three strains of *Escherichia communior* were used. The filtrates of young cultures of all these organisms were injected into a series of normal rabbits (denoted A in table 1) and the effects observed. The same filtrates then were injected into a second series of laparotomized animals (denoted B in table 1). Six rabbits, reported in table 1, and three others in the experimental series each received 3 or 4 cc. of plain broth about two hours prior to the injection of the toxic filtrates. We also gave two injections of plain broth but did not in any instance observe an effect that was abnormal. The plain broth was therefore harmless. We also observed normal rabbits for possible spontaneous reactions, but saw only normal rhythmic longitudinal movements and occasional peristalsis.

Meltzer and Auer<sup>2</sup> first introduced the term "peristaltic rush," in 1907. Before this, in 1872, the phenomenon had been described by van Braam van Houkgeest<sup>3</sup> as "Rollbewegungen." As stated by Meltzer and Auer, it is "a rapidly progressing wave of contraction preceded by a completely relaxed long section of the intestine through which fluid contents mixed with gas bubbles is rapidly driven. A complete peristaltic rush is one which sweeps down from the duodenum to the coecum without stopping." "Each coil, as the rushing wave passes through it, gives the appearance of a rapidly turning wheel."

Meltzer and Auer<sup>2</sup> did not see a rush in the opened abdomen of a normal rabbit. They also realized that "an opened abdomen is not a normal state." Alvarez and Mahoney,<sup>4</sup> however, claimed to have seen "good rhythmic movements and good spontaneous rushes shortly after the animals are opened." We saw an incomplete rush in only one supposedly normal rabbit injected with plain broth and this only when about two hours had elapsed following laparotomy. Rhythmic movements in the small intestine, and frequently also propulsion in the lower colon, were always seen by us in normal rabbits immediately following the operation, but spontaneous rushes were not seen.

2 Meltzer, S. J., and Auer, J. Am J Physiol **20** 259, 1907

3 Van Braam van Houkgeest Arch f d ges Physiol **6** 266, 1872

4 Alvarez, W. C., and Mahoney, L. J. Am J Physiol **69** 211, 1924

TABLE 1—General and Intestinal Reactions Produced in Rabbits Following Intravenous Injection of Young Culture Filtrates of the Colon-Typhoid Group of Organisms

Organism Used	Strain	Weight of Control Rabbit, Gm	Age of Culture, Hours	Dose of Filtrate Injected, Cc	Effect of Filtrate on Normal Control Rabbit (A)	Weight of Laparotomized Rabbit, Gm	Observed Reactions of the Intestines in the Laparotomized Rabbit After Injection of Filtrate (B)	Summary of Intestinal Reactions
Eberthella typhi (all newly isolated organisms received from Dr Charles Krumwiede)	E	2,100	17	4	1 10 slight defecation, 1 20 depression, rapid respiration and urination Survived	2,250	0 30 rapid respiration, 1 00 rapid, irregular respiration, 1 07 mild peristalsis in colon, 1 20 few fecal balls, quiescent thereafter	No definite excitation
	G	1,600	19	3, A, 4, B in A 2 hr 10 min and in B 1 hr 55 min after injection of 4 cc plain broth)	0 40 defecation, 0 45 considerable depression, urination Survived	2,300	0 25 rapid respiration, 0 55 mild pendulum movements in small intestine, 1 00 circular contractions of middle colon, complete relaxation of small intestine, 1 40 ceecum showed mild circular contractions and remained in fairly high tone, 1 15 middle colon spastic, showed longitudinal striations, 1 12 few fecal balls	No definite excitation
	R	1,360	23	3 (in A 2 hr and in B 2 hr 6 min after injection of 3 cc plain broth)	0 30 urination, 0 40 slight depression, defecation Survived	1,380	During two hours' observation, no change from normal	No definite excitation
Salmonella paratyphi A (stock strains)	O	2,600	17	4	0 55 urination, 0 67 mild diarrhea, depression, 0 70 rapid respiration, prostration, severe diarrhea, 1 25 improved Survived	2,170	0 12 normal pendulum movements of small intestine, 0 15 normal haustral movements in colon, 0 42 animal appears restless, lower colon spastic, 0 44 progressive increase of tone in small intestine, 1 00 part of small intestine appeared spastic and remained so	Mild effect on circular musculature
	L	1,650	18	3	0 20 urination, 0 35 prostration, rapid respiration, diarrhea 0 45 to 1 00 severe diarrhea, 1 15 depression Survived	1,700	1 12 marked peristalsis in ceecum and peristaltic rush in upper colon, lower colon spastic, 1 25 marked circular contractions in uterus, 1 33 longitudinal striations in small segment of colon, few fecal balls, 1 44 peristaltic rush in colon followed by rush in ileum filling ceecum, followed by marked cecal peristalsis, 1 45 antiperistalsis in colon, cecal movements, more defecation, 1 49 another peristaltic rush in colon contents fluid, 1 53 death in asphyxial convulsions (inspiratory spasm of diaphragm occurred prior to convulsions)	Peristaltic rushes in colon and ileum

Salmonella enteritidis (Gartner)	Wallasey (This caused an outbreak of food poisoning, the strain was supplied by Mr. Bruce White)	1,780	18	3 (in B 37)	0 10 rapid respiration, restless, 0 50 rapid, labored respiration, 1 10 prostration, 1 20 considerable defecation Survived	2,160	1 12 peristaltic rush throughout small intestine, defecation similar to control rabbit In a period of eighty minutes, five peristaltic rushes were observed, all of them completely emptying the small intestine into the cecum Colon spastic, showing haustral movements in middle colon Seventeen minutes after last rush, upper colon was dilated and showed kneading movements 1 02 peristaltic rush in small intestine, 1 10 second rush (incomplete), 1 12 diarrhea, 1 27 third rush, 1 29 rush of upper small intestine and middle colon, animal died 1 41	Peristaltic rushes in small intestine
	Delf (This was isolated at Delf, Su matra, and supplied to us by Prof E P Snyders)	1,850	18	3	1 00 marked prostration, urination and severe diarrhea Survived	2,130		Peristaltic rushes in small intestine and in middle colon
	D'nyasz 904 (A "D'nyasz", bacillus, isolated by R S Spray from commercial rat virus ATCC)	1,770	23	3 5	0 47 prostration, severe diarrhea Survived	2,160	0 40 peristaltic rush in upper small intestine followed by another one minute later (both incomplete), 0 50 peristaltic rush in colon, 0 52 second rush in colon, 1 07 peristaltic rush in small intestine filling cecum followed by rush in colon and defecation, respiration rapid and "jerky", 1 19 more defecation	Peristaltic rushes in small intestine and in colon
Salmonella schottmulleri	209 (rough strain from single cell culture)	1,600	18	3	0 49 urination, 0 50 prone, 0 55 defecation, 0 53 diarrhea, 1 05 more diarrhea (without marked prostration) Survived	2,400	0 25 strong contractions of uterus, 1 13 restless, 1 20 lower colon spastic, 1 30 lower colon showed contractions, intestine and uterus quiescent thereafter	No definite excitation
	B12 (both from collection of Prof E O Jordan)	2,220	20	3	0 50 rapid respiration, depressed, 0 55 diarrhea, 1 05 complete prostration Survived	1,710	0 33 marked pendulum movements throughout small intestine, 0 38 respiration deeper and more rapid, 0 48 pendulum movements very strong, 1 08 lower colon quite active, respiration "jerky", 1 13 strong propulsion in lower colon, middle colon spastic, no change thereafter	No definite excitation
Salmonella antrycke	185 (J Infect Dis 21 541, 1917)	1,700	24	3	0 45 prostration, urination, no diarrhea, 1 00 death in asphyxial convulsions	1,600	0 30 pendulum movements beginning in upper intestine, 0 45 respiration rapid and labored, marked peristalsis in upper colon, 0 55 defecation and urination, 1 20 respiration slower and deeper, peristaltic rush in small intestine followed by flaccidity, 1 24 strong peristalsis throughout small intestine, 1 26 death	Peristaltic rush throughout small intestine
	180 (J Infect Dis 21 541, 1917)	2,000	18	4	0 43 prostration, urination, 0 46 rapid respiration, remained prostrated for some time Survived	2,205	0 57 rapid respiration, 0 59 dyspnea, 1 17 peristaltic rush throughout small intestine followed by flaccidity, entire colon spastic, 1 23 second rush, 1 37 peristalsis in colon, upper part dilated, 1 45 third rush through small intestine, peristalsis in colon, 1 52 death in asphyxial convulsions	Peristaltic rushes throughout small intestine

TABLE 1—General and Intestinal Reactions Produced in Rabbits Following Intravenous Injection of Young Culture Filtrates of the Colony-typhoid Group of Organisms—Continued

Organism Used	Weight of Control Rabbit, Gm	Age of Culture, Hours	Dose of Filtrate Injected, Cc	Effect of Filtrate on Normal Control Rabbit (A)	Weight of Laparotomized Rabbit, Gm	Observed Reactions of the Intestines in the Laparotomized Rabbit After Injection of Filtrate (B)	Summary of Intestinal Reactions
Salmonella aertrycke (continued)							
Strain 683 (Carl Ten Broeck's strain, isolated from rabbits, "Rabbit typhoid no. 104," A.T.C.C.)	1,680	17	1	0 10 defecation, distress, 0 15 prostration, 0 50 respiration rapid and labored Survived	1,760	0 45 marked cecal movements, 1 00 peristaltic rush throughout small intestine, 1 38 defecation	Peristaltic rush throughout small intestine
de Nobele (from Prof E. P. Snyder's)	2,100	22	3 (in A 1 in 45 min and in B 1 hr 38 min after injection of 3 cc of plain broth)	0 25 depression, urination, 0 32 respiration labored, 0 40 marked prostration, 0 55 general tremors, died next day	2,225	0 25 to 0 32 several successive rushes throughout small intestine—extremely violent reaction—heart became irregular, 0 35 death in asphyxial convulsions	Peristaltic rushes throughout small intestine
Salmonella suis	1,950	19	4	1 25 depression, 2 05 marked depression, 2 30 slight defecation, improved, moderate reaction	2,000	1 25 incomplete peristaltic rush in small intestine, 1 27 peristalsis in small intestine, 1 45 peristaltic rush in small segment of small intestine	Incomplete peristaltic rush in small intestine
Tapioena (J. M. Research 43, 33, 1922)	1,310	17	3	0 50 depression, no other signs of reaction	1,810	Normal activity only observed	No definite excitation
Escherichia communior	1,850	18	4	0 40 marked distress, labored respiration, proceeding to complete collapse, which lasted for forty-minutes Recovered completely two days later	2,100	0 20 strong, propulsive in lower colon, 1 45 considerable defecation—dyspnea slightly more marked at times—no definitely abnormal reactions of intestine observed	No definite excitation
Blood (J. F. Per Med 4, 413, 1926)	1,650	18	1	0 55 urination, prostration, labored respiration Survived	2,250	During 2 hours occasional mild pendulum movements in small intestine, lower colon spastic with occasional periods of activity	No definite excitation
Stock strain	1,650	20	3	0 38 severe diarrhea, rapid respiration, no prostration, 1 13 labored respiration Survived	2,120	A change from the normal was not observed	No definite excitation

When the phenomenon occurred, it was induced by intravenous injection of a potent filtrate Alvarez and Mahoney's<sup>1</sup> method was also different from ours. They immersed the animal in a saline bath and pinched the intestines by means of serrefines attached to heart levers. They themselves realized that this may have changed the gradient. We may further add from our own experience that considerable amounts of fluid are taken up by the tissues within a short



Fig 3—A spasm produced in a loop of small intestine during the passage of a peristaltic rush induced following the intravenous injection of a filtrate of a young culture of a strain of *Salmonella aettrycke* (de Nobele)



Fig 4—Serial enlargements of a 16 mm moving picture film showing the passage of a peristaltic rush through part of a loop of small intestine, followed by relaxation. This reaction occurred following the injection of a filtrate of a young culture of a strain of *Salmonella enteritidis* (Delhi Sumatra)

time when saline or Locke's solution is used, which should be considered as a factor in increasing the fluid content of the intestine.

It is evident that the most violent reactions occurred in those groups actually concerned in the production of acute gastro-intestinal disturbance, i. e., *Salmonella enteritidis* (Gartnèr), *S. aettrycke* and

TABLE 2—*The Production of Peristaltic Rushes in the Rabbit's Intestine with Filthates of Young Cultures of the Colon-Typhoid Group of Organisms Correlated with the Generally Accepted Facts Concerning Disease Production by the Group (Modified After Snyder's and Bosch)*

	Salmonella paratyphi A (Brion and Kayser)	Salmonella enteritidis (Gartner)	Salmonella schottmulleri	Salmonella typhimurium	Salmonella supestrifer	Escherichia communior
Long incubation period, gradual onset, invades blood stream early	Much like typhoid, but may cause acute gastro intestinal disturbance, invades blood stream early	Always causes acute gastro intestinal disturbance, rarely invades the blood stream	Much like typhoid, invades the blood stream early, rarely produces acute gastro intestinal disturbance	Always causes acute gastro intestinal disturbance, rarely invades the blood stream	Much like typhoid, but may also produce acute gastro intestinal disturbance once invades the blood stream	Common inhabitant of the intestinal tract of man and animals, occasionally invades the blood stream, doubtful whether it causes acute gastro intestinal disturbance
Common in temperate zone and in tropics	More common in the tropics than in the temperate zone	Common in the temperate zone and in the tropics	More common in the temperate zone than in the tropics	Common in the temperate zone, not common in the tropics	Occasionally of importance in the temperate zone, endemic in Delhi (Sumatra)	Ubiquitous
Disease of man	Disease of man	Disease of man and of animals associated with man	Disease of man	Disease of man and of animals associated with man	Disease of man and swine (monkey? cattle?)	May cause disease in man and animals
Not implicated in food poisoning	Usually not implicated in food poisoning	Causes food poisoning	Not implicated in food poisoning	Causes food poisoning	May cause food poisoning	Not implicated in food poisoning
Strains used did not produce a peristaltic rush	One of two strains used produced a peristaltic rush	All strains used produced peristaltic rushes	Strains used did not produce a peristaltic rush	All strains used produced peristaltic rushes	One of two strains used produced a peristaltic rush	Strains used did not produce a peristaltic rush

*S. supestifer* (figs 3 and 4) *S. paratyphi* A (Brion and Kayser) also produced marked reactions in the lower intestine. *Eberithella typhi*, *S. schottmulleri* and *Escherichia communior* showed little if any effect on the intestine.

Table 2 shows the correlation of these observations with the known clinical aspects of infection with the groups in man and animal, modified and enlarged from the arrangement by Snyders and Bosch<sup>5</sup>. From this table it is clear that the organisms that usually cause food poisoning affect both man and animal. The group includes mainly *S. enteritidis* (Gartner), *S. aertnycke* and *S. supestifer*.

Some strains of *S. paratyphi* A (Brion and Kayser) may, under proper conditions, also produce the disturbance, but this subgroup usually is not implicated in the production of the disease. The first three forms, and particularly the first two, produce early in growth considerable amounts of diffusible toxic compounds. We have not seen evidence that the Schottmuller type of bacterium has been found associated with this condition.

One of us (Ecker) observed poor toxicity in filtrates of cultures of *S. aertnycke* grown in Cole's<sup>6</sup> medium. The organisms which previously formed smooth colonies were changed to a rough type, and their filtrates were practically atoxic. Some 40 liters of filtrates were lost. Cole stated that in his tryptic digest broth, diphtheria bacilli also failed to produce a potent toxin. A few outbreaks of food poisoning have been produced by *S. supestifer*. That it produces diffusible toxic substances in 2 per cent Witte peptone veal infusion broth was definitely demonstrated by Ecker and Richardson.<sup>7</sup> *S. supestifer* is also, however, according to Snyders, the cause of a typhoid-like disease at Sumatra, Dutch East Indies, and may produce acute gastro-enteritis.

Correlating the capacity of a young culture filtrate to produce a peristaltic rush in the rabbit with the generally accepted clinical observations, we noted with interest that severe reactions in the intestine of the rabbit were induced only with filtrates from those organisms that are linked with the production of acute gastro-intestinal disturbance (food poisoning). So far as we are aware, ours was the first observation that peristaltic rushes directly follow injection of bacterial products.

It has been observed previously, and may also be noted in table 1, that diarrhea did not necessarily accompany the severe reactions which occurred following the injection of toxic filtrates. The absence of

<sup>5</sup> Snyders, E. P., and Bosch, W. G. *Nederl. Tijdschr. v. Geneesk.*, vol. 4, 1928.

<sup>6</sup> Cole, S. W. *Practical Physiological Chemistry*, ed. 7, Cambridge, Eng., W. Heffer and Sons, 1926, p. 272.

<sup>7</sup> Ecker, E. E., and Richardson, M. L. *J. Infect. Dis.* **37**: 538, 1925.

diarrhea, however, may not be taken as evidence of the absence of intestinal reaction in the rabbit, as it was frequently observed that violent peristaltic rushes might fill the large saclike cecum with fluid while the greater part of the colon showed marked spasticity and prevented propulsion of the cecal contents beyond the upper part of the colon.

The method used in this study is being applied to other groups of intestinal organisms.

Of interest in this connection is the recent work of Koessler, Lewis and Walker,<sup>8</sup> who observed the effect of filtrates from bacterial growths in their study of pharmacologic action on arteries and bronchi. They found that, in a blood broth-glycerin-amino-acid medium, certain strains of many common pathogenic micro-organisms—pneumococci, streptococci, *Bacillus coli*, *B. typhosus* and *B. paratyphosus*—formed substances which caused arterial constriction in vitro and bronchial constriction in the living guinea-pig. They asserted that the action of the poisons was frequently selective. They also stated that filtrates that caused bronchiolar constriction sometimes did not have any action on the smooth musculature of the arteries, and vice versa. A spasm of both bronchi and arteries was, however, frequently obtained with the same filtrate. They claimed that in the majority of cases they dealt with poisons of unknown chemical constitution.

#### SUMMARY

A new method was devised for the observation and recording by motion pictures of intestinal motility in rabbits. The method was applied to the study of the colon-typhoid group of organisms, with particular reference to the effect of filtrates of young cultures on the intestines. The young culture filtrates of certain subgroups of the colon-typhoid group were found to produce violent intestinal reactions (peristaltic rushes and circular muscle spasms). The culture filtrates of those organisms commonly known as producers of food poisoning and which cause violent acute intestinal reaction in man (*S. enteritidis*, *S. aertrycke* and *S. suispestifer*) were found to be the ones which induced peristaltic rushes in rabbits, while culture filtrates of other organisms of the group, which may at times have been implicated in outbreaks of food poisoning (for example, *S. paratyphi* A) were variable in their effect. Some filtrates of organisms not definitely known to be associated with outbreaks of food poisoning (*Eberthella typhi*, *Escherichia communior* and *S. schottmulleri*) failed to produce a visible effect. It was further observed that the most effective filtrates were obtained from cultures of those types that cause disease in both man and animal (*S. enteritidis*, *S. aertrycke* and *S. suispestifer*).

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<sup>8</sup> Koessler, K. K., and Lewis, I. H. Determination of Bronchospasm in the Guinea-Pig, Arch. Int. Med. **39** 163 (Feb.) 1927.



# THE CIRCULATION OF BLOOD THROUGH THE SPLEEN PULP \*

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## THE BLOOD VESSELS OF THE SPLENIC LOBULE

In April, 1926, at the Albany Session of the Association of American Pathologists and Bacteriologists, sections of the spleen from human beings and from rabbits were demonstrated, showing in an apparently convincing manner the termination of arterial capillaries by opening out into the intercellular spaces of the spleen pulp of the marginal zone about the follicle <sup>1</sup> Further studies have fully confirmed these observations and have led to the recognition of an anatomic unit of spleen structure outlined by the most widely distended venous capillaries in the distended spleen, and this structural unit has been designated as the splenic lobule <sup>2</sup>

The central portion of the lobule is occupied by the malpighian corpuscle or splenic follicle. Around this is the marginal zone or intermediate zone of the lobule, characterized by the presence of small arterial capillaries in a close meshwork of reticulum and pulp cells and by remarkable freedom from venous capillaries. Peripheral to this zone, the pulp cords extend to the periphery of the lobule, separated from each other by venous capillaries or sinuses, which are largest at the border of the lobule.

The continuation of these studies, as opportunities have occurred, permits the presentation of some further evidence and may, perhaps, warrant the enunciation of certain conceptions in regard to the splenic circulation of man, which have heretofore been rather indefinite.

The follicle itself is provided with a rich supply of thin-walled capillary vessels given off from the follicular artery or its branches and anastomosing within the follicle and at its periphery. These capillary vessels finally terminate by short twigs which extend into the marginal

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\* From the Department of the Laboratories, New York Post-Graduate Medical School and Hospital

1 MacNeal, W J The Open Circulation of the Spleen Pulp, *Am J Path* **2** 473, 1926 MacNeal, W J, Otani, Sadao, and Patterson, Marjorie, B The Finer Vascular Channels of the Spleen, *ibid* **3** 111, 1927

2 MacNeal, W J The Splenic Lobule, *Contributions to Medical Science Dedicated to Aldred Scott Warthin*, Ann Arbor, George Wahr, 1927, p 525, abstr, *Arch Path* **3** 565 (March) 1927

zone and there become continuous with the intercellular spaces of the spleen pulp in this region. Under normal circumstances, therefore, these vessels permit the passage of plasma through their walls to bathe the structures of the follicle, but retain the formed elements of the blood and discharge them into the meshes of the marginal pulp. Within the follicle the pulp spaces are free from erythrocytes.

#### TYPES OF ARTERIAL CAPILLARIES

The marginal zone presents a sharp contrast to the follicle. Here there are abundant erythrocytes in the intercellular spaces of the pulp. In the spleen distended by perfusion, the marginal zone is seen to be free from venous capillaries. Arterial capillaries, however, are abundant here. They are of two kinds.

In the first class are those which represent terminations of the follicular capillaries. These are extremely narrow, and their walls consist of a single layer of thin endothelium. Some of them extend only a minute distance from the follicle before opening out into the pulp. This type was illustrated, not too clearly, by the photomicrograph, figure 2 of plate 42 in volume 3 of the *American Journal of Pathology* (1927) and by the drawing of the same structure shown in figure 13 of plate 48 in the same publication.<sup>1</sup> A similar capillary termination is shown in figure 1 of the present paper. The lumen of the capillary can be traced through the capsule of the follicle to become somewhat distended and then continuous with the intercellular spaces of the pulp reticulum. Sometimes it is possible to trace these follicular capillaries for a longer distance into the marginal zone, as is shown in figures 2 and 3, but they always terminate in the pulp at a considerable distance from the nearest venous capillary. In the human spleen, the termination is usually asymmetrical, so that the opening appears larger toward one side. The rod-shaped endothelial cells of the capillary wall become continuous with the reticular cells of the pulp. Sometimes their cytoplasm is spread out into a broad thin sheet at one side of the termination, as is shown in figure 3. The distended tip or terminal ampulla attains a diameter of only 10 to 15 microns in the preparations and is quite short. Sometimes it is possible to trace a follicular capillary to the marginal zone only to arrive at a blind end as the capillary walls come together (fig. 4). Erythrocytes are often found in the patent lumen of such a vessel. Evidently, these follicular capillaries function in an intermittent manner, as is known to be true of the cutaneous capillaries (Krogh<sup>2</sup>) and of the

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3 Krogh, August. The Supply of Oxygen to the Tissues and the Regulation of the Capillary Circulation, *J. Physiol.* **52** 457, 1918-1919, Studies on the Capillariomotor Mechanism, *ibid.* **53** 399, 1919-1920, Studies on the Physiology of Capillaries, *ibid.* **55** 412, 1921.

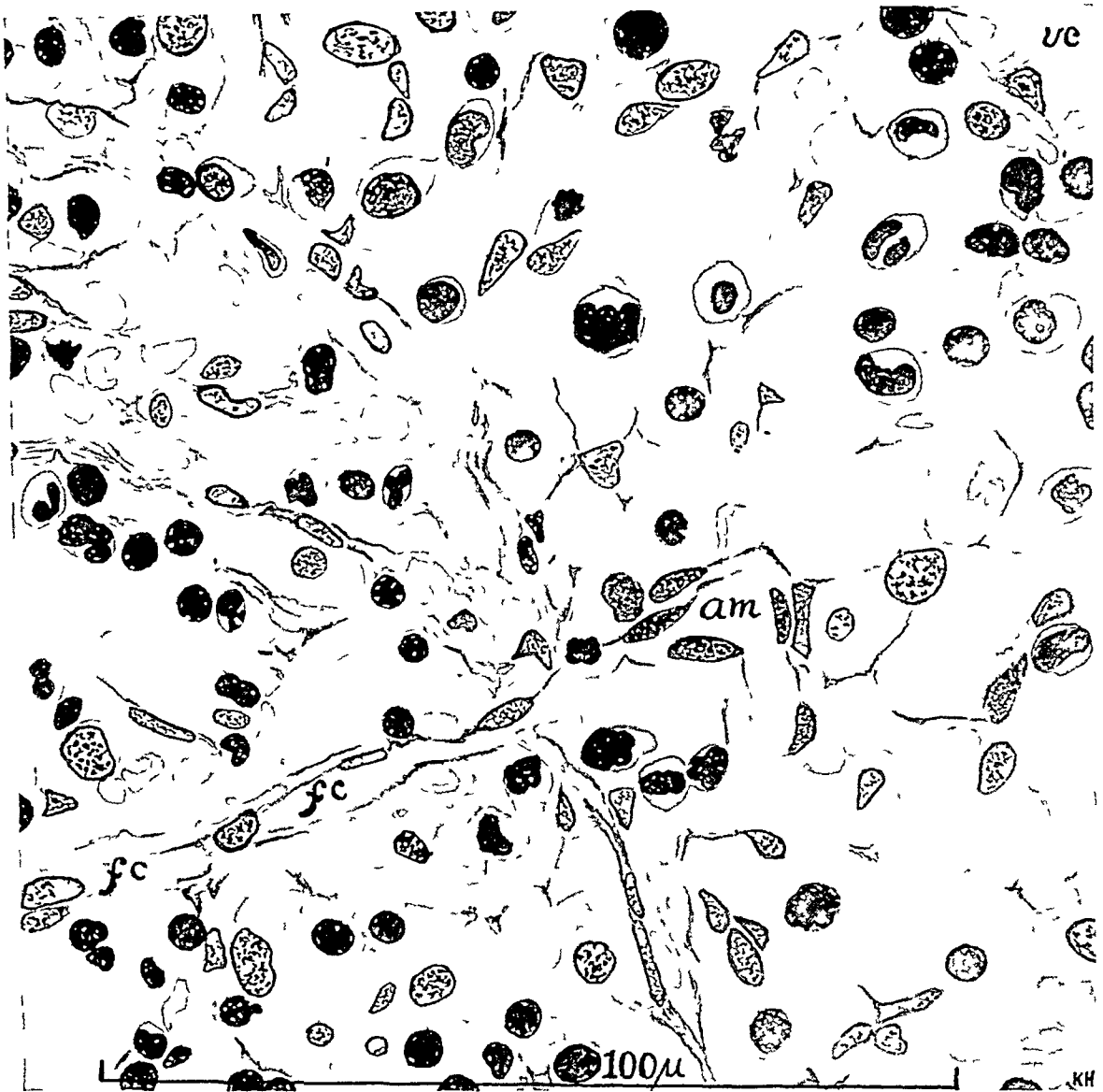


Fig 1—Spleen from a human being, termination of a follicular capillary in the marginal zone. The follicular capillary (*fc*) passes upward and to the right going through the capsule of the follicle slightly below the center of the figure to terminate in a slightly distended ampulla (*am*) in the pulp of the marginal zone. Here its lumen becomes continuous with the intercellular spaces of the pulp. The nearest venous capillary (*vc*) is seen at the upper right corner. The spleen was perfused three hours postmortem. It was the spleen of a boy, aged 8 months, who died of gangrenous inflammation of the mouth, pharynx and esophagus. Camera lucida drawing by Dr Kiyoshi Hosoi.

capillary tufts of the renal glomeruli (Richards<sup>4</sup>) In one vessel, the perfusion fluid is allowed to pass and distend the terminal portion as an ampulla, while another capillary remains collapsed at its tip or even for a large part of its course

The second kind of arterial capillary in the marginal zone is the centripetal capillary given off from the sheathed arterioles of the red pulp According to my observations up to the present, these sheathed arterioles are branches of the vessel which continues as the eccentric arteriole of its respective follicle I was unable to confirm the observation of Hueck<sup>5</sup> who found by reconstruction studies that sheathed

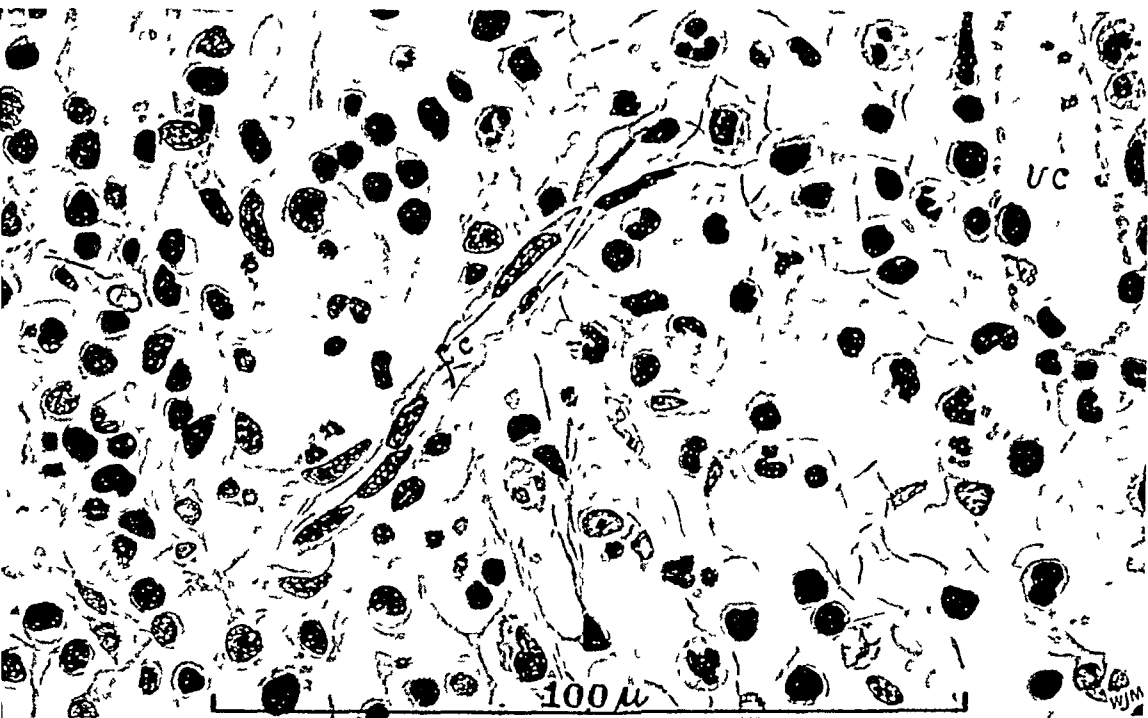


Fig 2—Spleen from a human being, termination of a follicular capillary in the marginal zone The follicle is at the left The follicular capillary (*fc*) passes upward and to the right to open out into the intercellular spaces of the pulp near the top of the picture The nearest venous capillary (*vc*) is seen at the upper right corner The spleen was removed at operation on a boy aged 7 years, with anemia, chronic purpura and thrombocytopenia It was perfused immediately after removal

arterioles coming from eccentric arteries of other follicles are present in the marginal zone These centripetal capillaries come out of the ellipsoids of Schweigger-Seidel as narrow vessels with extremely thin

4 Richards, A N The Nature and Mode of Regulation of Glomerular Function, *Am J M Sc* **170** 781, 1925

5 Hueck, W Ueber den Bau der Lymphknoetchen der Milz, *Verhandl d deutsch path Gesellsch* **22** 238, 1927

walls. Such a capillary usually branches quickly into two terminal twigs, which are directed obliquely toward the follicle and terminate in small ampullar dilatations which open out into the intercellular spaces of the pulp (figure 5). This type of termination was pictured in figures 4 and 14 of an earlier paper.<sup>1</sup> The present example is from another spleen in which the perfusion and fixation were more satisfactory. In the spleen of the rabbit, some of these centripetal capillaries appear to anastomose with the follicular capillary plexus. In the spleens of human beings, such connections have so far escaped my observation.

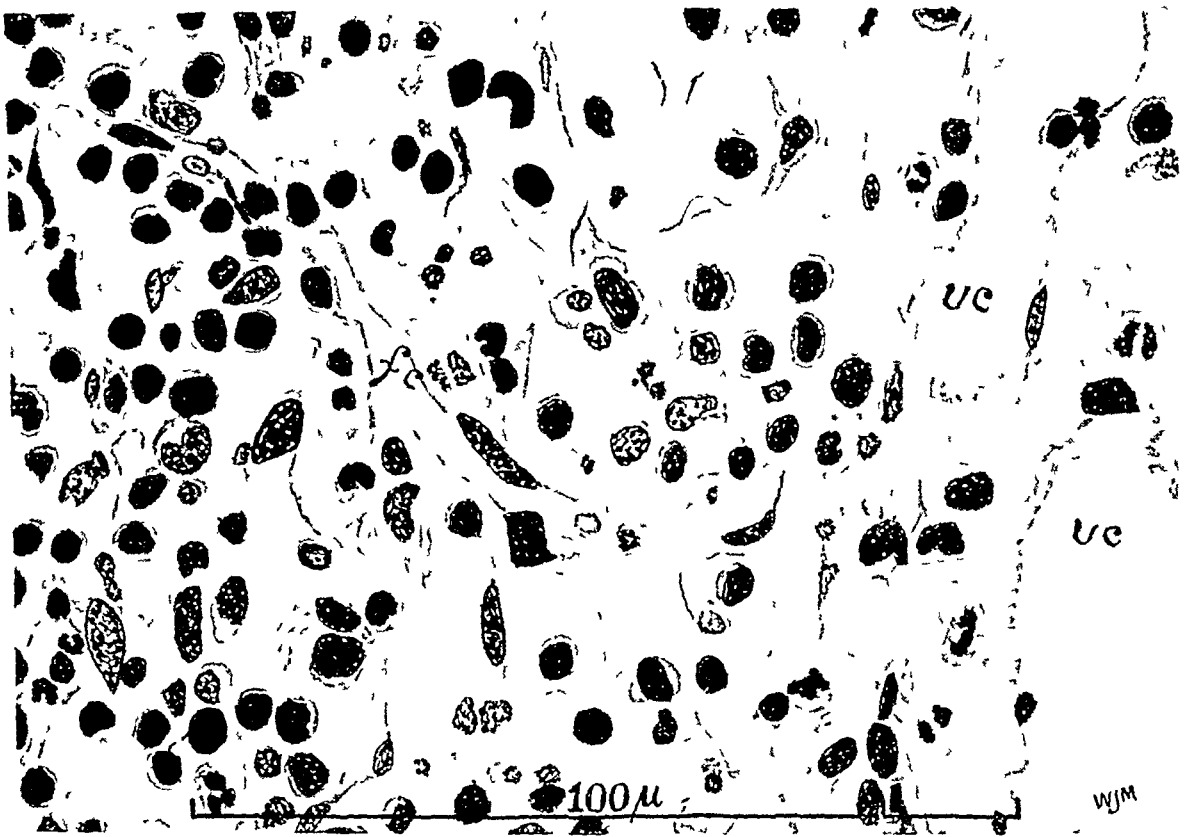


Fig 3—Spleen from a human being, termination of a follicular capillary in the marginal zone. The follicle is at the left of the drawing. The capillary (*fc*) terminates in the pulp just below the middle of the picture, and the nearest venous capillaries (*vc*) are seen at the right extending to the upper and lower corners of the drawing. Same spleen as in figure 2.

The third variety of arterial capillary of the human spleen is the arterial capillary of the pulp cord. This arises from a sheathed arteriole, as does the capillary just described. The same sheathed arteriole may give rise to several capillaries of both these varieties. The capillary of the pulp cord is longer than the others. It sometimes is quite straight, but often curves through the arc of a circle. For most of its course, it

lies well within a pulp cord, with a distinct layer of pulp reticulum between it and the nearest venous sinuses. At times, however, the capillary wall lies in contact with that of a venous sinus, and one may easily mistake such a contact for actual communication, if the section is thick and otherwise misleading. In thin serial sections, the arterial vessel will be found to pass along without opening into the venous sinus in its course. It may give off short lateral twigs which quickly terminate in the pulp reticulum. The main capillary terminates in a slightly distended irregularly asymmetrical ampulla which is situated in the midst

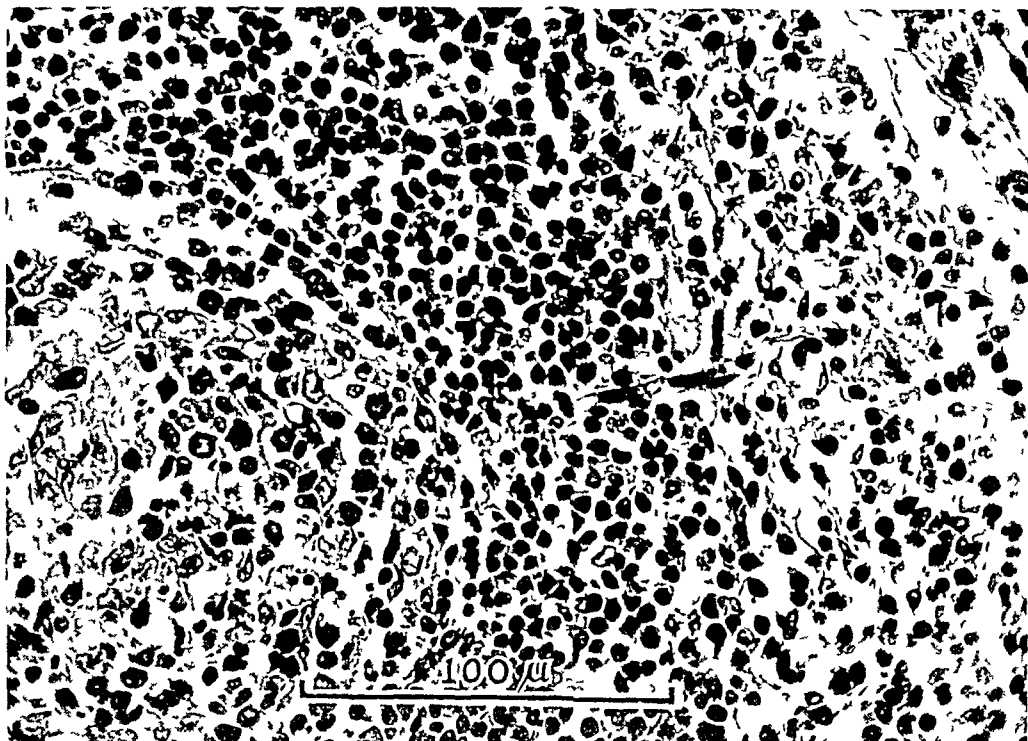


Fig 4—Photomicrograph of spleen from a human being. A follicular capillary is seen at the right of the center, running toward the right. This vessel is collapsed in part and could not be traced any farther in the adjacent sections of the series. The spleen was perfused two hours after death following a tonsillectomy in a well developed boy, aged 4 years. The measurement line represents 100 microns.

of a pulp cord as far as possible from the nearest venous sinuses (fig 6). An arterial capillary of this type was illustrated by figures 9 and 15 of an earlier paper<sup>1</sup>. Such capillaries are more easily recognized than the shorter ones previously discussed. They tend to run in a rather straight course, especially near the external capsule of the spleen, as has been pointed out by Neubert<sup>6</sup>.

<sup>6</sup> Neubert, Kurt. Der Uebergang der arteriellen in die venöse Blutbahn bei der Milz, *Ztschr f ges Anat u Entwicklungsgesch* 66:424, 1922.

Although the rabbit's spleen is much like that of man, there are distinct differences in the arterial capillaries. For example, in the long capillary of the pulp cord, the termination in the rabbit's spleen is a much more symmetrical and more definitely demarcated terminal ampulla, with a wall made up of many distinctly rod-shaped endothelial cells with large, oval, brightly staining nuclei. One of these is illustrated in figure 7. Here the plane of section has included the axis of the terminal portion of the vessel for a considerable stretch.

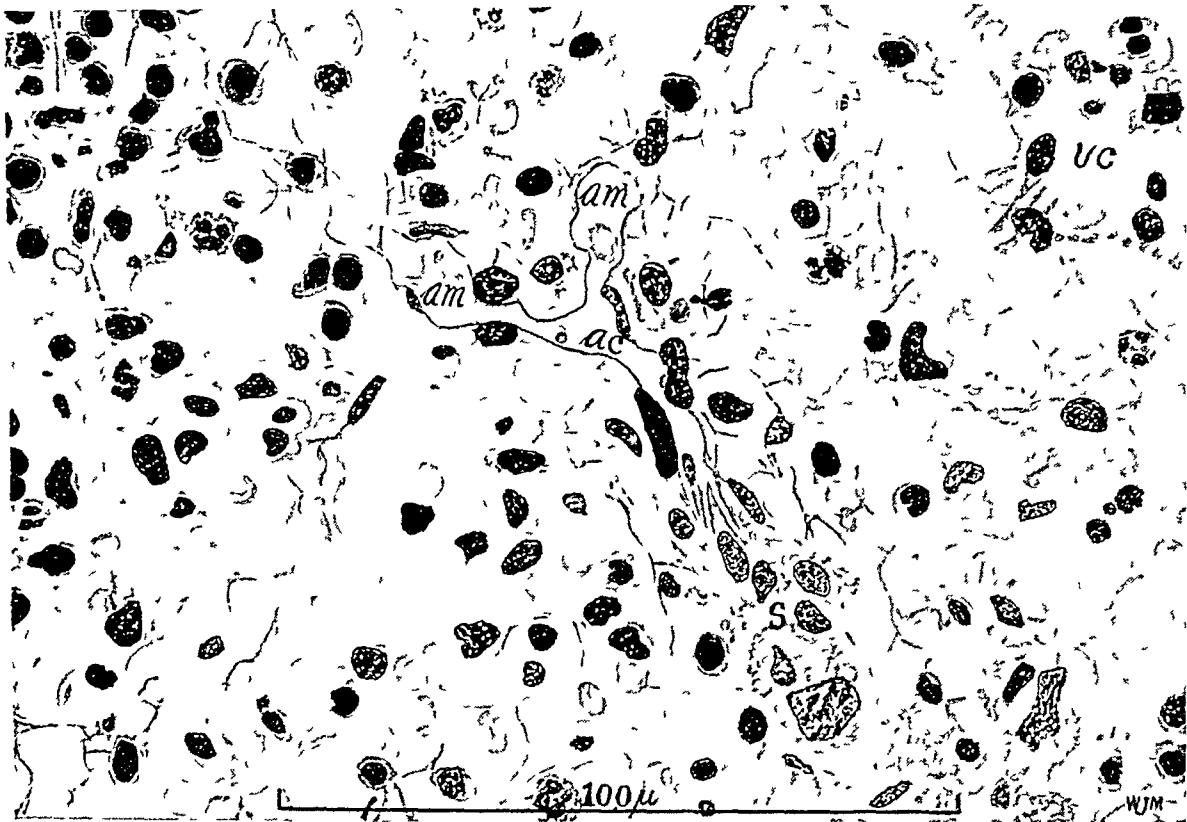


Fig 5—Spleen from a human being, centripetal arterial capillary of the marginal zone. The capillary (*ac*) extends upward and to the left from the lower margin of the drawing, the thick wall, constituting the sheath of Schweigger-Seidel (*s*), being cut at one side of the lumen. The lumen appears near the center of the drawing, and the sheath becomes indistinct and disappears. Near the termination, the thin-walled capillary divides, and the two branches become distended into ampullae (*am*), which open out into the intercellular spaces of the pulp of the marginal zone. The follicle is at the upper left corner of the drawing, its margin just appearing there. The nearest venous capillary (*vc*) is at the upper right margin of the drawing. Same spleen as that in figure 2.

The arterial ampullae of the spleen in man and of the rabbit's spleen here described and pictured are regarded as identical with the ampullae

described by Golz<sup>7</sup> and Thoma<sup>8</sup>. It is not so easy to identify them with the funnel-form ampullae described and pictured by Neubert<sup>6</sup> for the spleens of cats, swine and dogs. One is in some doubt whether the prolonged perfusion (from three to five hours) employed by Neubert may not have resulted in the rather extensive disintegration of the walls of the capillary terminations and thus have produced large spaces in the pulp surrounded by pulp reticulum. My observations on the spleens of the animals used by Neubert are still too limited to warrant a final opinion on this question.

#### THE VENOUS SYSTEM

The intercellular spaces of the pulp reticulum constitute the essential pathway through which the blood must pass from the terminations of

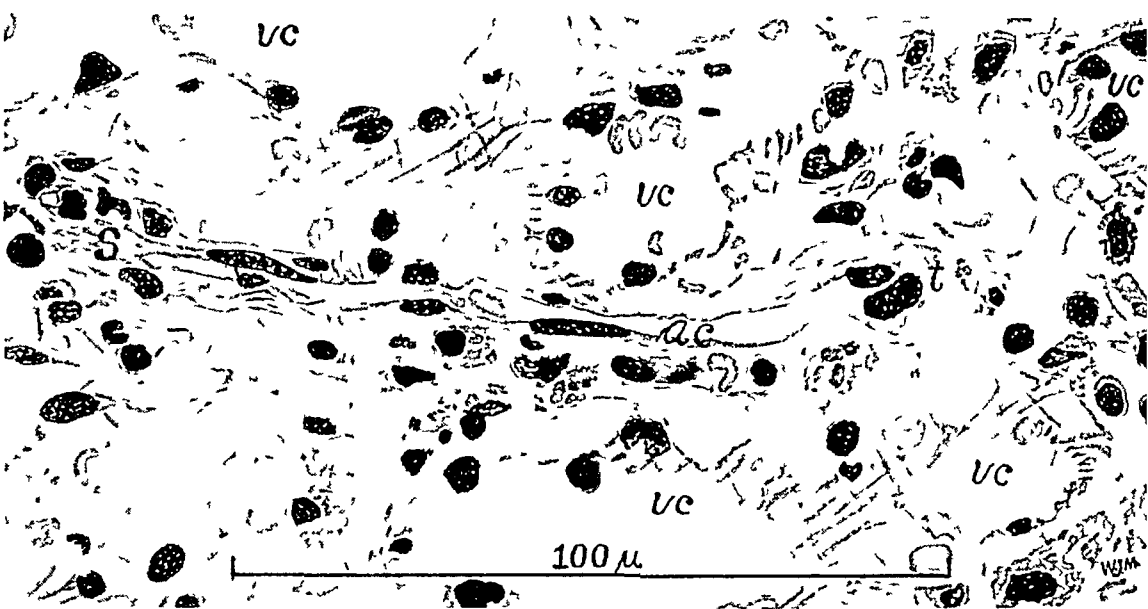


Fig 6—Spleen from a human being, arterial capillary of the pulp cord. The capillary (*ac*) extends from the left border almost to the right border of the picture. At either side of it are venous capillaries with fenestrated walls. The termination of the arterial capillary (*t*) is almost equally distant from three venous capillaries (*vc*). At the left, the arterial capillary has a thick sheath (*s*). Same spleen as that of figure 2.

the arterial capillaries to reach the first vessels of the venous system. This statement conforms to the view of those who have, for almost a century, maintained that the splenic circulation is an open circulation.

<sup>7</sup> Golz, Sigismund. Untersuchungen über die Blutefasse der Milz, Inaug. Diss., Jurjew, 1893.

<sup>8</sup> Thoma, R. Ueber die Blutefasse der Milz, Arch. f. Anat. u. Entwicklungsgesch., 1899, p. 267. Die normale Blutstrom und die venöse Stauung in der Milz, Virchows Arch. f. path. Anat. **249** 100, 1924.



The experimental demonstration of the immediate passage into pulp spaces of the spleen, of the erythrocytes of birds introduced into a short gastric branch of the splenic artery of a living rabbit, reported in March, 1926,<sup>9</sup> has brought strong support to this conception, to which there no longer appears to be any active opposition. Morphologic observations on serial sections may, therefore, now be more confidently employed to supply the detailed information in regard to this pathway. In the marginal zone, the direct opening of the terminal ampullae into the pulp spaces is easily seen and is distinctly shown in figures 1, 2, 3 and 5. In the arterial capillaries of the pulp cords, the openings into the pulp spaces appear somewhat smaller and are seen as openings in the wall of the ampulla between the endothelial cells, more irregularly arranged in man than in the rabbit. Blood cells are occasionally caught in transit from the arterial capillary to the pulp space. Everywhere in



Fig 7—Spleen of a rabbit, terminal ampulla of an arterial capillary of the pulp cord. The ampulla surrounded by pulp reticulum is shown at the center of the drawing. The nearest venous capillary (*vc*) is at the extreme upper left corner of the drawing. Section of a spleen perfused and fixed in the living animal.

the intercellular spaces of the red pulp one finds erythrocytes and other blood cells in intimate relation to the reticular cells of the pulp. It is here that phagocytosis of the blood cells is most abundant. Undoubtedly, the rate of passage is slow in these spaces and it is influenced not only by the arterial pressure but also by the contraction of muscle in the splenic capsule and trabeculae, and probably also by the contraction of the reticular cells and of the rod cells lining the venous sinuses, as has been suggested by Neubert<sup>6</sup> and by Foot<sup>10</sup>. From the pulp spaces, the

9 MacNeal, W. J., and Patterson, Marjorie, B. The Pathway of Nucleated Erythrocytes Introduced into the Splenic Artery, *Proc Soc Exper Biol & Med* **23** 420 (March 17) 1926.

10 Foot, N. C. The Reticulum of the Human Spleen, *Anat Rec* **36** 79 (July) 1927.

blood escapes into the venous sinuses through the fenestrations in the walls of the latter, the stomas of Mollier. These openings are easily recognized in any thin section of a well perfused spleen. They are illustrated in figures 2, 3, 6 and 8.

The venous system proper begins in a plexus of richly anastomosing channels, everywhere running between the pulp cords throughout the peripheral portions of the lobules. These channels are the venous sinuses. They are illustrated particularly in figures 6 and 8. Their walls are composed of rod-shaped endothelial cells with large oval nuclei that project into the lumen. These cells are sometimes attached to each other by protoplasmic processes but, in general, they are separated by parallel longitudinal clefts, which are crossed at intervals by slender

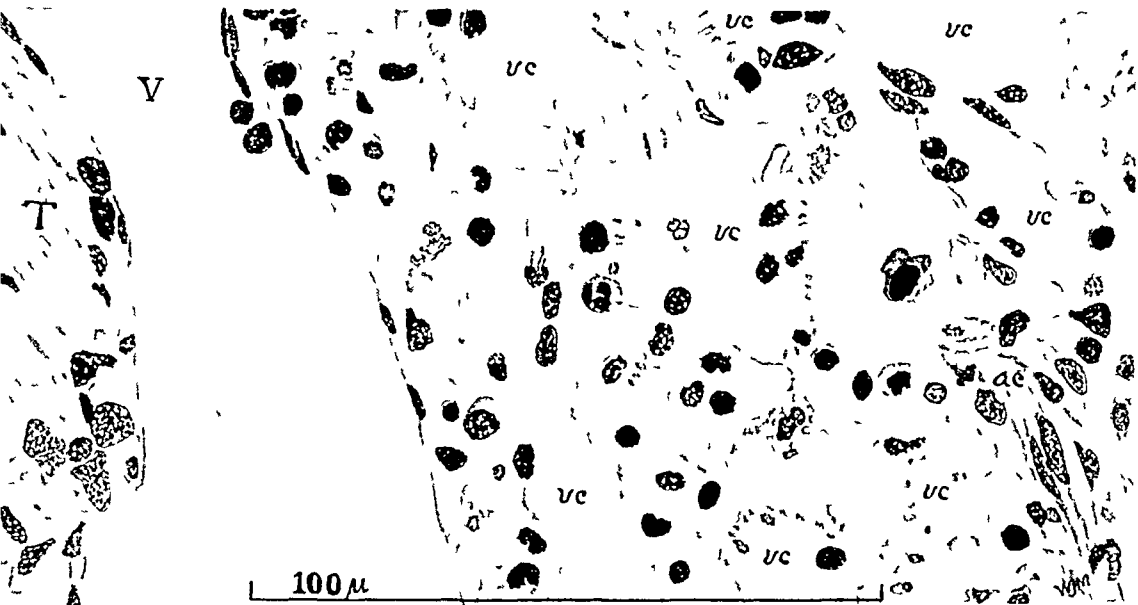


Fig 8—Spleen from a human being, pulp near the periphery of the lobule. Near the middle of the drawing one recognizes the venous capillaries (*vc*) of the pulp with their fenestrated walls lined by the rodlike endothelial cells, which have oval nuclei projecting into the lumen. To the left is seen a trabecula (*T*) and a larger vein (*V*), which is lined by a continuous layer of endothelium, the cells of which are flattened and contain flattened nuclei. An arterial capillary (*ac*) appears at the right lower corner of the drawing. Same spleen as that in figure 2.

reticular strands external to the rod cells and continuous with the pulp reticulum. The diagrammatic figure of Mollier, which has been so extensively copied, appears essentially correct. However, it should be noted that the caliber of a sinus is never the same for any considerable distance and that its course is tortuous, so that the diagram of a straight cylinder of even diameter may mislead the uninitiated. The sinus shown passing in a vertical direction in the middle of figure 8 is typical for the human spleen. This system of anastomosing sinuses opens widely near

the periphery of the lobule into small splenic veins, interlobular veins, which are lined by a continuous sheet of thin endothelial cells with flattened nuclei, distinctly different in form from the endothelial cells which form the walls of the sinuses. These veins come into relation with one of the trabeculae of the capsule, at first on one side, and later empty into the trabecular veins which lie within the substance of the trabeculae (fig 8)

#### PHYSIOLOGIC SIGNIFICANCE

The anastomosing network of fine thin-walled capillaries within the substance of the follicle is often entirely collapsed and blood-free in microscopic sections of undistended spleen. In the perfused spleen, these vessels may contain only cell-free fluid, although erythrocytes are occasionally seen in them. Hueck<sup>5</sup> thought that these minute vessels carry chiefly plasma. However, they come off rather directly from the eccentric arteriole or short intermediate branches of it. I am convinced that they carry blood, but that they tend to become empty rapidly with the fall of arterial pressure at death, by their own elasticity and because of the pressure of the surrounding follicular substance, which, during life, is distended by the arterial pressure in its interior. This capillary plexus provides a rich nutrition for the follicle. Through the thin capillary walls, the plasma evidently passes in considerable amount to the intercellular spaces of the follicle, coming into immediate contact with the reticular cells and with the proliferating lymphocytes. Toxic substances dissolved in the plasma are thus brought into intimate relationship with lymphatic cells, under conditions favorable for the chemical action of these cells.

The formed elements of the blood remain within the capillary lumen until they have reached the periphery of the follicle. There they pass through the open capillary ampullae directly into the intercellular pulp spaces of the marginal zone. Here is afforded an opportunity for a most effective testing of these formed elements. The contraction and dilatation of the pulp meshes subject them to physical pressure and distortion, as has been pointed out by Schmincke<sup>11</sup> and by Neubert.<sup>6</sup> Slowing of the current favors agglutination, and the intimate contact with the pulp cells permits phagocytosis of those formed elements destined for destruction.

The centripetal capillaries of the marginal zone furnish a rich nutritional blood supply to the periphery of the follicle, and they also discharge their formed elements into the intercellular spaces of the marginal zone. It is at once evident that this marginal zone about the follicle is

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11 Schmincke, A. Ueber die normale und pathologische Physiologie der Milz, *Munchen med Wchnschr* 63 (July 11) 1005, (July 18) 1047, (July 25) 1083, (Aug 1) 1118, 1916

the most important part of the lobule, as far as action on formed elements in the blood is concerned. Here phagocytosis of worn out blood cells and of foreign matter, such as microbes, occurs most abundantly.

In man, the centripetal capillaries come from arterial twigs enclosed in the ellipsoidal sheaths of Schweigger-Seidel. The physiologic significance of these curious sheath structures appears not to be fully elucidated. They doubtless have something to do with regulating the lumen of the arterial vessel in the interior, and thus regulate the relative amount of blood which may be delivered to the centripetal capillaries and the long capillaries of the pulp cords, as against the amount going to the intra-follicular capillary plexus, which is derived from arterioles without ellipsoid sheaths. The purpose subserved by such a regulation is not clearly revealed. Furthermore, it is not clear whether this mechanism is merely a local adaptation, whether it may be influenced by substances in the blood, such as hormones or drugs, or whether it is subject to nervous control. In the literature, one finds the suggestion that the ellipsoids serve as valves to prevent the reflux of blood from the pulp spaces into the arterial circulation. Assuming that the pressure within the pulp spaces might become greater than that within the arterial capillaries, it is nevertheless evident that all the splenic capillaries tend to collapse completely unless they are kept distended by arterial pressure greater than the pressure around them. One does not, therefore, need to recognize a special valvular action of the ellipsoids to explain the impossibility of perfusing a spleen in the reverse direction. I am not inclined to recognize this as a special function of the ellipsoids. The suggestion that the ellipsoids permit the passage of plasma through their substance and thus act chemically on dissolved substances in the fluid portion of the blood, somewhat as the follicles probably do, seems worthy of consideration. Adequate proof of this suggestion is lacking. Another possibility, which appears worthy of consideration, is suggested by the resemblance of the ellipsoid sheaths to the tissue of the follicles in the rabbit's spleen. Possibly the ellipsoids may be embryonic structures, capable of development into follicles as occasion may demand. A study of perfused fetal spleens might elucidate this point.

The long capillaries of the pulp cords terminate near the periphery of the lobule, with a thin layer of pulp between their terminations and the venous sinuses. Such an arrangement suggests that the blood cells passing through them escape into the veins without being subjected to much action of the spleen substance. These vessels are so long and slender, and their terminations are so far removed from the larger arteries, that any increase in pressure within the pulp, whether by passive congestion or by active contraction of the spleen, should result in their occlusion, thus forcing relatively more blood into the marginal zone about

the follicle. On the other hand, relaxation of the splenic musculature and low venous pressure would favor the passage of abundant blood through these longer capillaries, so that relatively more blood would escape the action of the splenic pulp of the follicle and of the marginal zone. Suggestions of this sort challenge experimental investigation. They may be of some significance in explaining pathologic changes in the structure of the spleen and especially in the localization of the parasitic microbes.

#### SUMMARY

1 It is possible to recognize a definite splenic lobule consisting of malpighian corpuscle, its marginal zone and the radiating pulp cords with the included vessels. The periphery of the lobule is marked by the widest venous sinuses in the distended spleen.

2 The arterial blood vessels of each lobule are terminal, without anastomosis with arterial vessels of other lobules. There are three kinds of capillaries: (1) the anastomosing capillary plexus of the follicle, which arises from the eccentric arteriole or a branch of it, (2) the centripetal capillaries of the marginal zone, which arise from a sheathed branch of the intralobular artery, (3) the long capillaries of the pulp cords, which arise from the same sheathed arteriolar branches.

3 The arterial capillaries of the follicle and the centripetal capillaries open out into the intercellular pulp spaces of the marginal zone at considerable distances from the nearest venous sinuses. The arterial capillaries of the pulp cords terminate in more or less well defined ampullae within the substance of a pulp cord, but separated from the adjacent venous sinuses by a thin layer of the pulp.

4 Apparently the arterial capillaries are patent only part of the time during life and all tend to collapse entirely at death. Perfusion and fixation in the distended state is essential in order to show the natural form and size of these vessels.

5 The anatomic arrangement of the spleen permits a partial separation of the blood plasma from the formed elements of the blood. The plasma comes into intimate relation with the lymphatic elements of the follicles, while the corpuscular elements come into immediate contact with the reticular cells of the red pulp. These relations appear to be of physiologic significance.

6 The venous system begins in a plexus of richly anastomosing sinuses found everywhere between the pulp cords in the peripheral portion of the lobule. They have fenestrated walls which permit the entrance of elements of the blood from the reticular spaces of the pulp.

# CHROMAFFIN CELL TUMOR OF THE SUPRARENAL MEDULLA (PHEOCHROMOCYTOMA) \*

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The chromaffin system as a tissue system was established by Kohn<sup>1</sup>. He based his conclusion that chromaffin tissues constitute a definite entity on the following facts, which apply wherever the tissues are found

- 1 They have a common embryonic origin—the anlage of the sympathetic ganglions—in both phylogenetic and ontogenetic development
- 2 They give a characteristic reaction to chromic salts (Henle)<sup>2</sup>
- 3 Extracts of these tissues possess the biologic property of causing a rise in blood pressure and glycosuria when inoculated into animals
- 4 They are indispensable in the maintenance of life

Tumors of this tissue are rare. They are of considerable interest. In their structure and location they bear out some of the facts that have been learned concerning the chromaffin system from which they arise. The possibility is presented that they are actively secreting tumors of an organ of internal secretion, the prolonged absorption of the secretion of which by the body causes the exaggerated biologic effects that are associated with these tumors.

It is for these reasons that this case is here reported, and since up to this time there has not been any systematic collection of cases of tumors of the chromaffin cells of the suprarenal medulla, all the available information concerning the reported cases, thirty in number, has been summarized, and a critical review of the many beliefs held in relation to certain aspects of their histologic constitution and associated clinical conditions has been added.

## EMBRYOLOGIC CONSIDERATIONS

For the better appreciation of the constitution and biologic aspects of these tumors, it would be well to recall certain facts concerning the development of the tissue from which they arise. The suprarenal cortex develops from the splanchnic mesoderm. Developmentally, and in most respects functionally, also, it may be considered a separate organ, it

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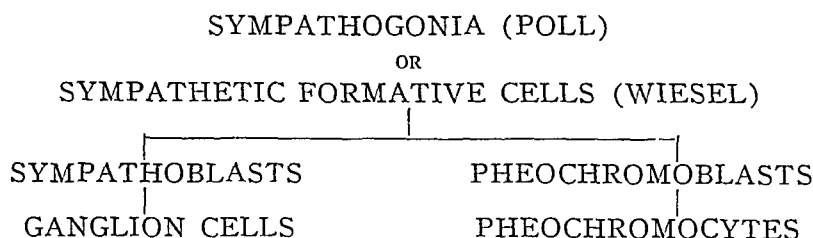
\* Submitted for publication, Sept. 17, 1928.

\* From the Laboratories of the Mount Sinai Hospital.

1 Kohn, A. Paraganglien, Arch f mikr Anat u Entwicklgs **62** 263, 1903.

2 Henle, J. Ueber das Gewebe der Nebenniere und der Hypophyse, Ztschr f rationelle Med **24** 143, 1865.

does not concern the present study<sup>3</sup> The immediate anlage of the suprarenal medulla, and the anlagen of the remainder of the chromaffin organs, lie in the sympathetic ganglions, which, in turn, are derived from the cells of the neural crest In the human 17 mm embryo may be seen the beginning of the migration of the primitive cells of these ganglions, the sympathogonia, or the sympathetic formative cells, laterally This migration continues during early fetal life In mammals, the sympathogonia migrate until they reach the cortical anlage of the suprarenal gland In the selachians, the migration ends just lateral to the aorta Migration is complete in the 85 mm embryo, at this time, they have taken up the position of the medulla<sup>4</sup> During the migration, portions of the embryonic tissue may become split off, these develop as separate organs at varying distances from the aorta in the region of the renal arteries or the inferior mesenteric artery to form the organs of Zuckerkandl<sup>5</sup> The further development of the suprarenal medulla consists in the process of differentiation from sympathogonia to the mature elements This may best be diagrammatically plotted<sup>6</sup>



This process of differentiation takes place in the last months of fetal life, and, according to Wiesel, is not completed until about the time of puberty<sup>7</sup> The sympathogonia, the parent cells of the sympathetic and pheochromic systems, are small round cells, slightly larger than lymphocytes, with each a scanty cytoplasm and a round, large nucleus containing a densely staining chromatin network These differentiate on the pheochromic side into larger cells, also round, with each a larger area of clear cytoplasm and a more vesicular nucleus The final stage of differentiation brings forth the mature pheochromocytes, which are large,

3 Kohn, A Ueber die Nebenniere, Prag med Wchnschr **23** 193, 1898

4 Wiesel, J Beitrage zur Anatomie und Entwicklungsgeschichte der menschlichen Nebenniere, Anat Hefte **19** 481, 1902

5 Zuckerkandl, E Ueber Nebenorgane des Sympathikus im Retroperitonealraum des Menschen, Verhandl d anat Gesellsch **15** 95, 1901

6 Poll, H Die vergleichende Entwicklung der Nebennierensysteme, in Hertwig Handbuch der Entwicklungsgeschichte der Wirbeltiere, Jena, Gustav Fischer, 1906, vol 3, p 442

7 Wiesel, J Bemerkungen zu der Arbeit H Kusters "Ueber Glome der Nebennieren," Virchows Arch f path Anat **180** 553, 1905

irregular or polyhedral cells, with each a round or ovoid vesicular nucleus, containing a loose chromatin network, and a well formed nucleolus. The cytoplasm is abundant and usually finely granular. In contradistinction to the pheochromoblasts, the pheochromocytes have the peculiar property of staining brown with chromic salts. It is the abnormal proliferation of these mature cells that makes up the tumor of the suprarenal medulla variously known as chromaffin tumor, paraganglioma or pheochromocytoma. The other groups of tumors arising from the suprarenal medulla, the neuroblastomas and ganglioneuromas, are derived from cells developing along the other line, comprising the nervous or nonspecific elements of the suprarenal glands.

#### REVIEW OF THE LITERATURE

The first report of a medullary tumor of the suprarenal gland that may be considered a pheochromocytoma was that of Berdez in 1892, who described a vascular, encapsulated tumor within the medulla of the right suprarenal gland.<sup>8</sup> Like most of the tumors reported subsequently, it did not replace the entire medulla but was demarcated from the remaining normal medullary tissue. Two years previously, Perley<sup>9</sup> had reported such a tumor, but his description of it is too meager to make one certain of its nature. Manasse,<sup>10</sup> in 1893, reported a tumor observed by him three years previously which showed the characteristics of a pheochromocytoma. He found the typical hyaline inclusions that one sees in the normal suprarenal medulla, noticed some cells that he considered as probably ganglion cells and also noted tumor cells in the suprarenal veins. Three years later, he reported a second case in which he demonstrated the chromaffinity of the cells composing the tumor.<sup>11</sup> Marchetti<sup>12</sup> was the first to describe a bilateral pheochromocytoma of the suprarenal medulla, in 1904. Suzucki,<sup>13</sup> in 1909 and 1910, reported three cases, one of which was necrotic and cystic. His was the first case reported as occurring in conjunction with neurofibromatosis. He also noted the pres-

8 Berdez. Contribution a l'etude des tumeurs des capsules surrenales, *Arch d med expér et d'anat path* **4** 414, 1892.

9 Perley, cited by Herxheimer. *Beitr z path Anat u z allg Path* **57** 115, 1914.

10 Manasse, P. Ueber die hyperplastischen Tumoren der Nebennieren, *Virchows Arch. f. path. Anat* **133** 391, 1893.

11 Manasse, P. Zur Histologie und Histogenese der primären Nierengeschwulste, *Virchows Arch f path Anat* **145** 127, 1896.

12 Marchetti, G. Beitrag zur Kenntnis der pathologischen Anatomie der Nebennieren, *Virchows Arch f path Anat* **177** 227, 1904.

13 Suzucki, S. Ueber zwei Tumoren aus Nebennierenmarkgewebe, *Berl klin Wchnschr* **47** 1623, 1910, Ueber einen chromaffinen Tumor des Nebennierenmarks, *ibid* **46** 1644, 1909.



ence of sympathetic formative cells Laignel-Lavastine and Aubertin<sup>14</sup> in the same year noted the occurrence of melanoderma in their cases Neusser and Wiesel,<sup>15</sup> in 1910, reported the unusual occurrence of this tumor in a 2 year old child, who had the vascular changes of an epinephrine sclerosis, and at the same time they included a case of Kolisko's, the first in which signs of vasomotor instability were noted Herde,<sup>16</sup> in discussing two cases of his, considered the tumors to be hamartomas in the sense of Albrecht<sup>17</sup> In 1913, Helly<sup>18</sup> reported a case with hypertension and glycosuria without renal or pancreatic disease A year later, Hedinger<sup>19</sup> reported a case associated with cystic degeneration and suggested the name struma medullaris cystica suprarenalis Harbitz,<sup>20</sup> in 1915, reported a chromaffin cell tumor of the suprarenal gland as occurring in conjunction with a hypernephroma L'abbé, Tinel and Doumer<sup>21</sup> observed a case with the clinical syndrome of paroxysmal hypertension The first tumor of this nature to be removed at operation was the case of Masson and Martin<sup>22</sup> The patient died of shock, which the authors considered incommensurate with the severity of the operation Recently, Riemer<sup>23</sup> reported a cystic tumor of this type in association with Addison's disease Furthermore, malignant tumors, as evidenced by the formation of metastases, were described by Bonnamou,

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14 Laignel-Lavastine and Aubertin Adenome medullaire de la capsule surrenale (medullome surrenale) chez un tuberculeux melanodermique, Arch de med exper et d'anat path **20** 818, 1908

15 Neusser, E, and Wiesel, J Die Erkrankungen der Nebennieren, ed 2, Vienna, Alfred Holder, 1910, p 97

16 Herde, M Zur behre der Paragangliome der Nebenniere, Arch f klin Chir **97** 937, 1912

17 Albrecht Ueber Hamartome, Verhandl d deutsch path Gesellsch **7** 153, 1904

18 Helly, C Zur Pathologie der Nebenniere, Munchen med Wchnschr **33** 1811, 1913

19 Hedinger, E Struma medullaris cystica suprarenalis, Frankfurt Ztschr f Path **7** 112, 1914

20 Harbitz, F Tumors of the Sympathetic Nervous System and the Medulla of the Suprarenal Glands, Especially Malignant Neuroblastomas, Arch Int Med **16** 324 (Aug) 1915

21 L'abbe, Tinel and Doumer Crises solaires et hypertension paroxystique en rapport avec une tumeur surrenale, Bull et mem Soc med d hôp de Paris **46** 982, 1922

22 Masson, P, and Martin, J F Paragangliome surrénale, etude d'un cas humain de tumeurs malignes de la medullo-surrenale, Bull de l'Assoc franç p l'etude du cancer **12** 135, 1923

23 Riemer, R Sobre un caso de syndrome de Addison produzio por "Paraganglioma da capsula supra-renal," Folha med **8** 33, 1927

Doubrow and Montequé<sup>24</sup> and Masson<sup>25</sup> The former quoted a description of another malignant case, from Gravier and Bernheim Other tumors of this kind illustrating the characteristics of structure and a variety of associated clinical conditions were described by the following authors Kawashima,<sup>26</sup> Wegelin,<sup>27</sup> Herxheimer,<sup>28</sup> Orth,<sup>29</sup> Thomas,<sup>30</sup> Bergstrand,<sup>31</sup> Biebl and Wichels,<sup>32</sup> Zwecker,<sup>33</sup> Oberling and Jung<sup>34</sup> and Schroeder<sup>35</sup>

*Pheochromocytoma of Other Chromaffin Organs*—These tumors are not confined to the suprarenal medulla They may occur wherever chromaffin tissue is found The first tumors of this nature to be noted in the carotid gland were described by Marchand<sup>36</sup> and by Paltauf<sup>37</sup> Since that time, about eighty tumors in this location have been reported The organ of Zuckerkindl was involved in a number of reported cases, the first was reported by Stangl,<sup>38</sup> and the latest by Handschin<sup>39</sup> To this

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24 Bonnamour, Doubrow and Montequé Sur le comportement des metastases pleurales des paragangliomes, Ann d'anat path **4** 141, 1927

25 Masson, P Tumeurs Traité de pathologie medicale et de thérapeutique applique XXVII, Diagnostics de Laboratoire II, Paris, A Maloine et fils, 1923, p 596

26 Kawashima, K Ueber einen Fall von multiplen Hautfibromen mit Nebennierengeschwulst, Virchows Arch f path Anat **203** 66, 1911

27 Wegelin, C Ueber einen chromaffinen Tumor der Nebenniere, Verhandl d deutsch path Gesellsch **15** 255, 1912

28 Herxheimer, G Ueber Tumoren des Nebennierenmarks, Beitr z path Anat u z allg Path **57** 112, 1914

29 Orth, J J Ueber eine Geschwulst des Nebennierenmarks nebst Bemerkungen ueber die Nomenklatur der Geschwulste, Sitzungsber d deutsch Akad d Wissensch, Berlin, G Reimer, 1914, no 1

30 Thomas, E Ein chromaffine Tumor der Nebenniere Ein weitere Beitrag zu den Markgeschwulsten der Nebenniere, Frankfurt Ztschr f Path **16** 376, 1915

31 Bergstrand, H A Case of Pheochromocytoma of the Suprarenal Gland with Hypertrophy of the Myocardium of the Left Ventricle, Hygeia **83** 321, 1920

32 Biebl, M, and Wichels, P Physiologische pathologisch-anatomische Betrachtungen in Anschluss an einen Fall von Pargangliom beider Nebennieren, Virchows Arch f path Anat **257** 182, 1925

33 Zwecker, I T Chromaffine Tumor of the Adrenal Medulla, Boston M & S J **192** 254, 1925

34 Oberling, C, and Jung Paraganglioma de la surrenali avec hypertension, Bull et mem Soc med d hôp de Paris **10** 366, 1927

35 Schroeder Doppelseitiges Nebennierenparagangliom, Centralbl f allg Path u path Anat **41** 483, 1927-1928

36 Marchand, F Beitrage zur Kenntnis der normalen und pathologischen Anatomie der Glandula carotica und der Nebennieren, Beitr z Wissensch Med Festschr f Virchow, 1891, vol 1, p 535

37 Paltauf, R Ueber Geschwulste der Glandula carotica, Beitr z path Anat u z allg Path **11** 260, 1892

38 Stangl, E Zur Pathologie der Nebenorgane des Sympathicus, Verhandl d deutsch path Gesellsch **5** 250, 1902

39 Handschin, E Zur Kenntnis den Zuckerkindlschen Organe, Beitr z path Anat u z allg Path **79** 728, 1928

group possibly belongs the case associated with paroxysmal hypertension in which operation was performed by Mayo<sup>40</sup> Alezais and Peyron<sup>41</sup> described a chromaffin cell tumor in the sacrococcygeal region and gave the name paraganglioma to the entire group, considering it a neoplasm of the paraganglion, as described by Kohn<sup>1</sup>

Pheochromocytomas of the supiarenal medulla in animals were described by Stilling<sup>42</sup> and by Zangfrognini<sup>43</sup>

#### REPORT OF A CASE

*History*—A Polish woman, aged 45, when admitted to the Mount Sinai Hospital, on June 3, 1927, complained of a cough that had troubled her for four months. For ten years, she had had palpitation and dyspnea on slight exertion and a tremor of the hands. She had been considered as having exophthalmic goiter and had been treated by means of roentgen rays for a suspected substernal goiter. She had been unsuccessfully operated on a number of times for sterility. For the past few years, she had been vomiting about once a week. This had become more frequent, so that, for from four to five months before admission, she had been vomiting almost nightly.

*Examination*—A physical examination disclosed a moderate degree of exophthalmos, a marked tremor and hypertrichosis of the chin. Her blood pressure on several examinations varied from 226 systolic and 108 diastolic to 177 systolic and 122 diastolic. During her stay in the hospital, her temperature ranged from 103 to 104 F. A week after her admission, she began to exhibit twitchings of the hands and face, and she lapsed into a semistuporous state. Her neck was stiff and Kernig's sign was positive. The pupils were markedly contracted. The nitrogen content of the blood was normal. The meningeal signs became more marked, and she died in coma.

The clinical diagnosis was Grave's disease and chronic nephritis with hypertension.

*Autopsy* (by Dr Paul Klemperer)—The body was well developed. There was hypertrichosis of the chin. The eyes were slightly bulging.

*Chest*—The lower lobe of the right lung was completely shrunken. It was composed of dense, white connective tissue, in which were seen a few areas of lung tissue. The pleura was densely adherent. The bronchus of the right lower lobe was extremely stenosed. There were several hemorrhagic infarcts in the left lower lobe. The branch of the pulmonary artery leading to this lobe contained a riding embolus, the ends of which showed fresh thrombi extending distally.

*Heart*—The pericardial sac was covered with a bilobed, fleshy thymus. The heart weighed 515 Gm. There were numerous ecchymoses in the epicardium. All the chambers were hypertrophied and somewhat dilated. There was a slight

40 Mayo, C. H. Paroxysmal Hypertension with Tumor of Retroperitoneal Nerve, J. A. M. A. **89** 1047 (Sept 24) 1927.

41 Alezais and Peyron. Un groupe nouveau de tumeurs epitheliales. Les paragangliomes, Compt rend Soc de biol **38** 745, 1908.

42 Stilling, M. H. A propos de quelques experiences nouvelles sur la maladie d'Addison, Rev de med, Paris **10** 808, 1890.

43 Zangfrognini, A. Adenoma di tessuto cromaffine della capsula surrenale, Sperimentale, Arch di biol **58** 812, 1903.

thickening at the line of closure of the mitral valve, but not any evidence of old or recent endocarditis. There was a slight sclerosis of the right coronary artery. The left coronary artery was wide. The pulmonary artery showed lipid patches. The aorta had lost its elasticity. Its intima showed yellow sclerotic patches throughout its extent. The peripheral vessels showed a slight intimal thickening.

**Spleen, Liver and Suprarenal Glands.** The spleen weighed 110 Gm, and showed evidence of chronic passive congestion. The liver weighed 1,025 Gm. It was firm and brown, with a distinct lobular structure. The right suprarenal gland was the seat of a tumor, which will be described later in detail. The left suprarenal gland was normal in shape and position. Its cortex measured 12 mm in width. The medulla was from 3 to 4 mm wide.

**Kidneys.** The right kidney weighed 170 Gm. It showed a distinct flattening of its upper pole. The capsule stripped with ease, revealing a smooth brown surface, which showed numerous small ecchymoses. On section, it did not show any abnormality. The left kidney weighed 135 Gm. On section, it showed a few sharply defined hemorrhagic areas within the cortex. There was a red thrombus in the renal vein.

**Gastro-intestinal Tract, Thyroid Gland, Pancreas, Ovaries and Uterus.** The gastro-intestinal tract disclosed a few small polyps of the large intestine. The thyroid was small and granular. The pancreas appeared normal. The right ovary was wrinkled, small and fibrous. The left ovary was missing. The uterus was small and atrophic. Its endometrium was atrophic.

*Microscopic Examination*—**Thyroid.** The acini of the thyroid gland were filled with pink and bluish colloid. The septums were fibrous. The epithelium was low. Evidence of hyperplasia or lymphocytic infiltration was absent.

**Lungs.** The lungs were congested. There was an area of hemorrhagic infarction with a thrombus at its apex. The arterial walls were thickened. The right lower lobe showed the acini replaced by dense acellular connective tissue with thickened, almost completely obliterated arteries, partly recanalized. There were occasional medial calcifications. Within this fibrous tissue there were many glandlike structures with low cuboidal epithelium.

**Aorta, Heart and Pulmonary Artery.** There was intimal proliferation of the aorta with lipid changes. The media showed calcification and small round cell foci. The adventitia showed arteriosclerosis of the nutrient vessels and narrowing of their lumen. The heart showed hypertrophy of the muscle fibers. There was a slight arteriosclerosis of the branches of the coronary arteries. The pulmonary artery showed a moderate degree of intimal proliferation.

**Liver.** The liver showed central hyperemia with necrosis of the hepatic cells. There was a conspicuous arteriosclerosis of the branches of the hepatic artery. Some of the smaller arterioles were hyalinized.

**Pancreas and Spleen.** In the pancreas, thickening and hyalinization of the small arterioles were noticeable. The spleen showed marked arteriosclerosis and congestion.

**Kidneys.** The kidneys revealed moderate arteriosclerosis of the arcuate and interlobular arteries, and conspicuous hyalinization of the arterioles. Most of the glomeruli did not show any changes, but a number of them contained hyaline material within the tufts. A few of these glomeruli showed markedly engorged capillaries. There was intense congestion in the region about these glomeruli. The tubular epithelium, in general, was not altered except in the regions of the infarcted glomeruli, where epithelial necrosis was encountered.

**Suprarenal Gland and Brain** The left suprarenal gland showed the medulla abundant. Within the medulla were a considerable number of round cell foci. The cortex was wide and rich in lipoids. The brain did not show any changes. The meninges did not show any evidence of inflammation.

#### THE TUMOR

The right suprarenal gland was unusually large and round. It lay on the upper pole of the right kidney, which was flattened. On section, almost the entire structure was seen to be replaced by a round encapsulated tumor, 4 cm. in diameter. At the upper pole there was a cap of suprarenal cortex and medulla, normal in appearance. Surrounding the tumor was a fibrous capsule, which blended with the yellow cortex. At the medial surface was a projecting portion



Fig 1—A section of the right suprarenal gland showing the encapsulated tumor with a well preserved cortex. Above the tumor is a cap of normal suprarenal gland with normal medulla. To one side there is normal medulla separated from the tumor by the capsule. (Natural size.)

of cortex and wide medulla, which was demarcated from the encapsulated tumor. The tumor tissue was rather soft, homogeneous and reddish brown, it showed areas of hemorrhage.

**Microscopic Examination**—The capsule, which was rather thick, consisted of connective tissue and flattened cortical cells. The cortex in most places was flattened. Separated from the tumor by the capsule were two areas of medullary tissue, which presented a normal appearance. The tumor consisted of anastomosing cords and islands of large polyhedral cells irregular in shape and varying from 15 to 45 microns in diameter. The cytoplasm, which was abundant, appeared finely granular and stained bluish red with hematoxylin-eosin. In formaldehyde-fixed specimens, the cells varied in their affinity for hematoxylin.

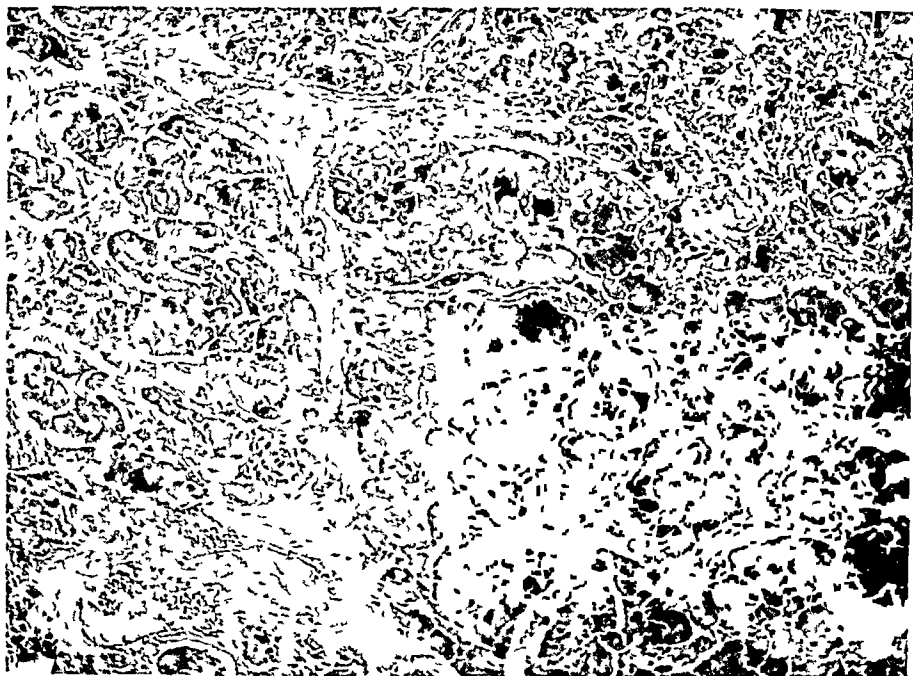


Fig 2—Islands of cells separated by vascular stroma The scattered darker cells show the chromic reaction (Magnification,  $1 \times 200$  )

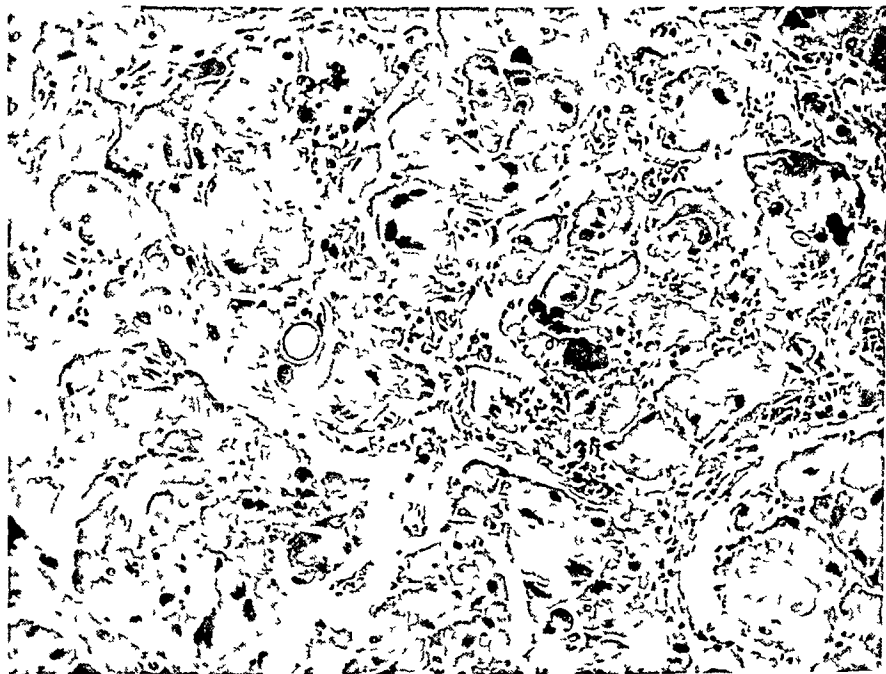


Fig 3—Higher magnification of the same field as shown in figure 2, showing the lack of stroma between the cells of the alveolae, their syncytial arrangement, their varying size, the shape and the staining qualities of the nuclei and the colloid inclusions (Magnification,  $1 \times 400$  )

Scattered cells were markedly basophil and stained deeply with hematoxylin. The same variance was shown in the specimens fixed in formaldehyde-Muller. After fixation with chromic salts, the cytoplasm of some of the cells stained yellowish brown. This yellow-brown color was independent of the granulation of the cytoplasm. It was present between the granules. In specimens stained with carmine, the yellow-brown color showed up especially well and appeared to be present in the nuclei and in the nucleoli. The nuclei were large, some were round, some oval and some rather irregular. They varied in their staining capacity, most contained a dense chromatin network and were pyknotic, some were vesicular. In general, the nuclei took a deeper stain than those in the normal medulla. They contained one or more distinct, large, round nucleoli. Within the cytoplasm, and also between the cells, there were occasional large and small spherical and ovoid bodies, which stained deeply with eosin and had a hyaline appearance. They did not react with chromic salts. They stained blue with Mallory's aniline blue and were not affected by Mallory's phosphotungstic acid hematoxylin. Rarely, there were found scattered among the typical cells of the tumor, single large, bizarre cells, each measuring about 70 microns and containing a large, irregular, deeply staining nucleus and a clear cytoplasm, which did not show the chromic reaction.

In places, there was an infiltration of the stroma by leukocytes and plasma cells, occasionally, by small cells, larger than lymphocytes, with scanty cytoplasm, the nuclei of which showed a dense chromatin network. These might possibly be considered as sympathogonia. The cords and islands of cells were separated by numerous capillaries and fine strands of connective tissue, which in places also showed the chromic reaction. There were many small hemorrhagic areas, and areas of vacuolar degeneration and necrosis of the tumor tissue. Sudan stain showed the absence of fat. Iron pigment was absent. One of the larger veins contained a fresh thrombus. A number of the veins contained tumor cells.

*Chemical Examination*—A portion of the tumor was macerated in saline solution and the extract examined for the presence of epinephrine qualitatively by the method of Ewins.<sup>44</sup> It showed a strongly positive reaction. Examined quantitatively by the method of Folin, Cannon and Dennis,<sup>45</sup> the tumor, which weighed 40 Gm, was found to contain 1.5 mg of epinephrine per gram of tumor tissue. The total epinephrine content of the tumor, as shown by this method, would therefore be 60 Gm. The organ was removed seven and a half hours after death, and the test was carried out on the following day. Since epinephrine is rapidly destroyed in the tissues after death, the epinephrine content during life might have been considerably greater.

#### SUMMARY OF THE CASE

The case, then, was that of a woman, aged 45, who for many years had been suffering from hypertension together with nervous manifestations similar to those of exophthalmic goiter. She had fever for about one week, developed signs of meningitis and died in coma. At autopsy, there were found a marked hypertrophy of the heart, generalized arterio-

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<sup>44</sup> Ewins, A. J. Some Color Reactions of Adrenine and Allied Bases, *J. Physiol.* **40** 317, 1910.

<sup>45</sup> Folin, O., Cannon, W. B., and Dennis, W. A New Colorimetric Method for the Determination of Epinephrine, *J. Biol. Chem.* **13** 477, 1912-1913.

sclerosis and arteriosclerosis, chronic passive congestion of the viscera, infarcts of the lungs and a pheochromocytoma of the medulla of the right suprarenal gland. The suprarenal tumor showed areas of necrosis and hemorrhage with venous thrombi.

Although there were pathologic evidences of cardiac insufficiency, the clinical picture was not that of death due to cardiac failure. In the absence of lesions of the brain or the meninges to account for the meningeal symptoms, and in the absence of a focus of inflammation to explain the fever, the similarity of the clinical condition to cases of suprarenal hemorrhage as described in the literature suggests the possibility that necrosis and hemorrhage within the tumor caused death in this case.

#### REVIEW OF OTHER REPORTED CASES

Thirty other cases of tumors of this type are reported in the literature. The reports reveal facts of such clinical and pathologic interest that it is thought wise to make them more available by means of the following summary.

*Occurrence with Regard to Sex and Age*—The tumor occurred more often in women than in men, namely, in eighteen women and in six men. The incidence was greatest in older people. The first five cases reported were in persons over 60 years of age. Subsequent reports showed its predominance in the fourth, fifth and sixth decades. Neusser and Wiesel<sup>1</sup> described a case in a 2 year old infant.

*Location*—Thirteen were in the right suprarenal gland, nine were in the left and six were bilateral. Kolisko's case (cited by Neusser and Wiesel<sup>1</sup>) showed, in addition, a third tumor, separated from the suprarenal gland, a chromaffin cell tumor over the right kidney, evidently a tumor of a medullary rest. Harbitz<sup>20</sup> reported a tumor of the left suprarenal gland associated with an additional tumor of a similar nature over the left kidney.

*Gross Appearance*—The largest tumors were those reported by Suzucki<sup>13</sup> and Hedinger<sup>10</sup>. They measured 10 cm in diameter both were cystic. The smallest tumors reported were the size of a pea. The smaller tumors were grayish in appearance, the larger ones were red and hemorrhagic, and sometimes dark brown, as a result of old hemorrhages. They were located distinctly within the medulla and were well encapsulated, the cortex being thinned out over them.

The cases of Berdez, Suzucki, Laignel-Lavastine and Aubertin, Wegelin, Herde (case 2), Thomas, Biebl and Wichels, as well as the case I have reported showed the presence of a normal medulla separated from the tumor by a capsule. The tumors often showed hemorrhages and were prone to undergo partial necrosis and to become cystic (Suzucki, Kolisko, Herde [2 cases], Hedinger, Thomas, Riemer). Often the cysts were multiple.

*Microscopic Appearance*—The microscopic picture in other reported pheochromocytomas agrees, in general, with that in my case. The tumors consisted either of nests or of cords of polyhedral cells separated by thin connective tissue stroma, rich in capillaries, giving the tumors either an alveolar or a trabecular appearance. Nine cases were described as trabecular, six cases as having a definite alveolar formation and three cases as showing both types of arrangement in different portions of the tumor. The predominating element of these tumors was always described as a polyhedral cell, somewhat larger than the cell of the



normal suprarenal medulla, and having an abundant, finely granular cytoplasm, varying greatly in size, and a rather large nucleus containing a chromatin network which stained more deeply than that of the normal vesicular nucleus seen in the normal medulla. Mitoses were rare. Most of the cases contained many multinucleated cells. The nuclei showed one or more large nucleoli. Single large bizarre cells with giant pyknotic nuclei were observed in many of the cases. Hedinger considered the possibility of their being ganglion cells. They did not, however, show any of the characteristics of ganglion cells except for their size. In all cases, the affinity of the cells for chromic salts was variable. The chromaffin cells were scattered between similar cells which took the chromic stain little or not at all.

The presence of hyaline inclusions within the cells of the tumor was first noted by Manasse, and since then the hyaline inclusions have been seen in most of the cases. They have the appearance of the inclusions seen in the cells of the normal suprarenal medulla, but are much larger.

Manasse, Wegelin and Thomas described a diffuse brown staining of the interstitial tissue by the chromic salts. Suzucki and Herde noted that the cytoplasm of the pheochromocytes was stained brown diffusely between the cytoplasmic granules.

Ganglion cells, together with unmyelinated nerve fibers, were noted by Marchetti and Hedinger. Cells with pyknotic nuclei, having the appearance of sympathogonia, were described in half the reports of cases. The difficulty of differentiating these from ordinary lymphocytes makes it hazardous to force an explanation of their presence.

Manasse and Biebl and Wichels found many of the specific cells within the larger veins. Suzucki observed a chromaffin cell in an artery and brown masses within the veins.

*Epinephrine Content*—Qualitative tests for epinephrine were performed chemically or biologically on extracts of the tumor tissue in a number of the reported cases. In all cases so examined, the presence of epinephrine was demonstrated. Quantitative determinations were not made.

*Glycogen*—The presence of glycogen was variable. Thus, Herde was able to demonstrate the presence of glycogen in his first case but not in his second. Hedinger reported a similar experience.<sup>46</sup>

*Associated Conditions*—Certain clinical observations in the reported cases deserve mention. Thus neurofibromatosis as a concomitant condition was observed in four cases (Suzucki, Kawashima, Herxheimer, Zwecker). Hypertension independent of renal disease was present clinically in nine of the latest twenty cases (those reported by Neusser and Wiesel, Helly, Orth, Bergstrand, L'abbe, Tinel and Doumer, Biebl and Wichels, Oberling and Jung, Schroeder, and the one reported here). Neusser and Wiesel's case was in a child, aged 2 years. In two additional cases, in which a clinical report was not recorded, there were pathologic evidences of hypertension. Thus, in the case of Thomas, there was hypertrophy of the left ventricle, and in Herde's case 2 there were hypertension and cardiac hypertrophy, with a primary, genuine contracted kidney. Recently, paroxysmal hypertension was observed by Oberling and Jung and by L'abbe, Tinel and Doumer. The patients in these cases were only 28 years of age. Four cases of glycosuria have been described (Herde's case 1, the cases of Helly, Biebl and Wichels, L'abbe, Tinel and Doumer). In the first two,

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46 Hedinger, E., in discussion of Wegelin (footnote 27)

mention is not made of the condition of the pancreas, and in the other two the pancreas is described as having been normal grossly and microscopically."

A number of the cases presented symptoms of vasomotor or sympathetic instability, or shock. Thus, Kolisko's patient died two hours after the administration of a 25 per cent solution of cocaine preceding the extraction of a tooth. Herde's patient died shortly after the simple amputation of a gangrenous extremity. Masson's patient died, after the removal of the tumor, in deep shock, which, in the opinion of the author, was incommensurate with the operative trauma. Oberling and Jung's patient went into shock and died immediately after a normal delivery. Helly's patient died after an operation for fistula in the anus and for hemorrhoids, under local anesthesia. A case that deserves special mention was that of a patient of L'abbe, Tinel and Doumer. A woman, aged 28, exhibited attacks of paroxysmal hypertension, each ushered in by an intense emotional reaction. The attacks were accompanied by marked pallor and tremor and were followed by nausea, a sense of constriction in the abdomen and vomiting, with urinary suppression. Pressure on the eyeballs caused a drop in the blood pressure from 280 to 104 and was followed by generalized vasodilation and glycosuria. The patient suffered two attacks of pulmonary edema.

Another pathologic condition of interest associated with pheochromocytoma was the colloid adenoma of the thyroid found together with a large adenoma of the liver by Hedinger. Still another was that found by Harbitz, in examining a tumor of the left suprarenal gland, namely, a cystadenoma of the pancreas and a hypernephroma of the left kidney with a pheochromocytoma between that kidney and the tumor-containing suprarenal gland—a combination in one case of hyperplasias of misplaced rests of both the suprarenal cortex and the medulla.

*Arteriosclerosis was found regularly in the cases associated with hypertension.* Neusser and Wiesel considered the arterial lesions in their case (medial necrosis) as typical of suprarenal sclerosis. Biebl and Wichels discussed the significance of arteriosclerosis in these cases at length. They believed that a direct relationship between the tumor and the clinical manifestations is evident. They explained the absence of medial necrosis in the lesions produced experimentally with epinephrine as due to the differences between the human and the animal subject. While this explanation may be valid with respect to the absence of medial necrosis, it does not afford evidence that the arteriosclerotic lesions are caused by a hyperadrenalinemia. In the absence of the specific medial lesions, one must consider the arteriosclerosis as more probably due to the mechanical effect of the hypertension.

#### COMMENT

From the foregoing facts, one may draw certain conclusions concerning this type of tumor. It is, without doubt, a neoplastic growth of a portion of the suprarenal medulla. The perfect encapsulation and the presence of a normal medulla outside of the tumor show that it is not a diffuse medullary hyperplasia.

Usually, the tumor is benign. It is perfectly encapsulated, does not give rise to metastases and does not cause a cachectic state. Those who feel that it is malignant mention the irregular size and character of the cells, and the tendency to hemorrhage and degeneration. These proper-

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47 Recently, Schroeder reported a case with glycosuria and atrophy of the pancreas.

ties may be more properly evaluated, however, when one considers the structure of the tissue from which the tumor arises, which also possesses similar characteristics. Nevertheless, as has been mentioned, malignant tumors of a similar nature have been reported. The available information concerning them is meager, especially in respect to the epinephrine content of the tumors and their metastases.

Various authors have considered the tumor as a hamartoma (Herxheimer, Herde, Dietrich<sup>48</sup>). There is considerable evidence against this view. The tumor evidently arises from a mature cell—the pheochromocyte—and occurs in persons of middle age and old age, when the process of differentiation of pheochromocytes from sympathogonia has been completed. The malignant embryonal tumors occur before puberty, the time when maturation is complete (Wiesel). Encapsulation is not a characteristic of the hamartomas, which are embryonal malformations and do not belong to the group of new growths (Albrecht). In regard to similar tumors in misplaced suprarenal rests (Harbitz, Weichselbaum and Greenisch<sup>49</sup>), one may rightly consider the conception of hamartoma, but not in the case of a tumor arising from mature elements in their normal location.

Degeneration, necrosis and cyst formation are characteristic of these tumors. The cyst fluid has never been tested for the presence of epinephrine. It seems probable that among the growths reported as cysts of the suprarenal gland there are a number that are really cystically degenerated pheochromocytomas.

It is evident that the tumor is actively secretory. Microscopically, the chromaffin reaction, as shown by Ogata,<sup>50</sup> is direct evidence of the presence of a strong reducing substance, which is, in all probability, epinephrine. This substance exists in a fluid state. It is independent of the cytoplasmic granules of the pheochromocytes. It permeates the cells and the surrounding tissues.

The cellular structure is similar to that of the normal suprarenal medulla. The hyaline inclusions seen in the normal suprarenal medulla have been repeatedly found in the tumor. I have shown that in their staining reactions with phosphotungstic acid hematoxylin and Mallory's aniline blue they do not show any resemblance to similar droplets that are the products of degeneration nor in fact to other hyaline types of

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48 Dietrich, A., and Siegmund, H. Die Nebenniere und das chromaffine System, in Lubarsch and Henke. Handbuch der speziellen pathologischen Anatomie, Berlin, 1926, vol. 8, p. 1049.

49 Weichselbaum and Greenisch. Das Adenome der Niere, Wien med. Jahrb., 1883, p. 221.

50 Ogata, T., and Ogata, A. Ueber die Henlesche Chromation der sogenannten chromaffinen Zellen und den mikrochemischen Nachweis des Adrenalins, Beitr. z. path. Anat. u. z. allg. Path. **71** 376, 1923.

degeneration Furthermore, I have been able to confirm Biebl and Wichels' observation that they are best seen in the better preserved portions of the tumor These observations speak strongly against the theory that the droplets are degenerative in nature The additional fact that they are found within cells of a secretory type indicates that they are products of secretion That they do not show the histochemical reactions of epinephrine leads one to the hypothesis that they represent an intermediary phase of the secretion of epinephrine

The epinephrine content, as shown by chemical and biologic tests, gives further proof that the tumor secretes The amount of epinephrine in this case, as shown by quantitative examination, was far greater than that reported in normal suprarenal glands

Outstanding in this review is the large percentage of cases associated with hypertension and signs of vasomotor or autonomic instability The occurrence of hypertension at an early age, the inability of so many of these patients to withstand minor operative procedures and the sudden death without demonstrable cause in this case appear also to be more than simple coincidences Furthermore, the occurrence of glycosuria demands explanation It is well known that epinephrine can cause such clinical manifestations, and it is tempting to assume that these manifestations are due to the action of the epinephrine that has been shown to be secreted by the tumor That it really is the cause of the clinical symptoms in the cases here reviewed, however, can be proved only by the demonstration of an increased absorption of epinephrine from the tumor The only evidence available in this connection is the vascularity of the tumor, which suggests the possibility of absorption

Manasse<sup>51</sup> and Biebl and Wichels, who observed cellular constituents of the tumor within the veins, considered that a pressor substance might be transmitted in this way In fact, the former considered this the mechanism for the distribution of epinephrine from the normal suprarenal gland However, one should not lay too much emphasis on the importance of this observation Liver cells singly and in groups are seen repeatedly within the portal veins in microscopic sections I have even seen an entire glomerulus in one of the branches of the renal vein, and Suzucki reported the finding of a chromaffin cell in an artery in his case Such observations lead one to conclude that this is probably the result of a technical artefact and to minimize the validity of the conclusions drawn from it Anatomic proof of the absorption of epinephrine is lacking

Chemical proof of the causal relationship between the clinical states and the tumor would consist in the demonstration of hyperadrenalinemia

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51 Manasse, P Ueber die Beziehungen der Nebennieren zu den Venen und dem venösen Kreislauf, Virchows Arch f path Anat **135** 263, 1894

However, such a demonstration is impossible with the present methods. A similar difficulty lies in the way of proving that increased absorption of epinephrine is the cause of hypertension. The presence of increased amounts of epinephrine in the suprarenal glands in hypertension has been reported by a number of workers.<sup>52</sup> However, in addition to other conflicting facts that discredit the theory, is the fact that increased absorption of epinephrine has not been demonstrated.

It is perhaps advisable to offer some justification for the term pheochromocytoma. The tumor has been known variously by the names angiosarcoma, perithelioma, struma medullaris cystica suprarenalis, paraganglioma and chromaffin cell tumor. The first three names may be excluded for obvious reasons. The term paraganglioma was originated by Alezais and Peyron in 1907 in describing a tumor of the sacrococcygeal region. It was derived from the name paraganglion, which was applied by Kohn to the chromaffin system, appropriate since it described the embryonic origin of the system. Pick,<sup>53</sup> however, suggested the advisability of naming the tumor from the predominating type of cell—in this case the pheochromocyte, the name of which, originated by Poll, is generally accepted. It appears especially advisable to use the name of the mature chromaffin cell, because of the parallelism between this tumor and the ganglioneuroma, which was named after the mature sympathetic cell, which is developed from the same anlage.

#### SUMMARY AND CONCLUSIONS

A case of pheochromocytoma of the suprarenal medulla associated with hypertension is reported. This tumor is benign. It arises from the mature pheochromocyte. It is not a hamartoma.

The hyaline droplets found in the cells of the tumor as well as of the normal suprarenal medulla are differentiated from the hyaline droplets of degeneration by the staining reactions. The droplets probably represent an intermediary state of the secretion of epinephrine. The tumor is actively secretory. Quantitative examination shows that it contains a total amount of epinephrine much in excess of that which is found in normal suprarenal glands at autopsy.

A large percentage of the cases reported in the literature presented clinical symptoms that might well be explained as due to the absorption of excessive amounts of epinephrine. That these clinical conditions are really caused by the action of epinephrine absorbed from the tumor can be proved only by the demonstration of an increased concentration of epinephrine in the blood.

<sup>52</sup> Dietrich, H., and Siegmund, H. (footnote 48, p. 994)

<sup>53</sup> Pick, L. Das Ganglioma embryonale sympathicum, Berl klin Wchnschr 49 16, 1912

# THE EFFECT OF ELECTRIC CURRENTS ON THE ARTERIES

A HISTOLOGIC STUDY <sup>\*</sup>

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AND

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It is still a matter of discussion whether electric currents in passing through the body produce typical anatomic changes or whether these changes are merely the result of the heat into which the electric energy is transformed in a conductor of the resistance of the living tissues. This question has been taken up especially with regard to the so-called current markings of the skin, and most investigators, including those who emphasize their diagnostic value, consider them an effect of the high temperature at the point of entrance and exit of the current, which causes a coagulation and boiling of the tissues.

The arterial lesions found in the vicinity of electric burns are of great practical importance, since they may lead to severe hemorrhages, hours or even days after the accident, and since they often make ligation of the injured blood vessel impossible. Jellinek<sup>1</sup> called attention to the great fragility of the arteries in and around electric wounds. Balkhausen and Gruter described an extensive destruction of the nuclei of the media of the arteries. Martin Couvert and Dechaume observed a disintegration of the muscular elements of the media of the arteries associated with a separation of the internal elastic membrane from the media. Dickens found severe inflammatory changes in the arteries of both forearms following an injury by lightning stroke. Bolongnesi reported microscopic observations of the blood vessels of rabbits through the hind limbs of which a domestic current had been sent. There were multiple ruptures of the elastic fibers with thrombosis and hemorrhages.

The importance of the subject and the scarcity of the available data induced us to perform a series of experiments in which arteries of dogs were exposed to electric currents. Low tension currents only were used because they produce changes which lend themselves better to a microscopic analysis than the severe destructions that result from currents of high voltages.

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<sup>\*</sup> From the Department of Pathology, University of Illinois.

1 For the literature, reference should be made to the senior writer's review on electropathology, Arch Path 5 837, 1928.

Since in experiments of this nature the technic is of great importance, it will be described in some detail

# METHODS

The experiments were performed under sterile conditions on adult dogs. Under ether anesthesia, the femoral artery below Poupart's ligament was dissected out for a distance of 5 cm. A small branch, found usually near the lower end, was ligated and cut. A thin rubber sheet was spread underneath the artery in order to isolate it as much as possible. Twisted strips of gauze soaked with a physiologic saline solution served as electrodes. They were wound around the vessel twice without constricting it, and were placed at a distance of 2.5 cm in such a manner that at each end there remained a free arterial segment at least 1 cm in length. This precaution was necessary in order to avoid too great a

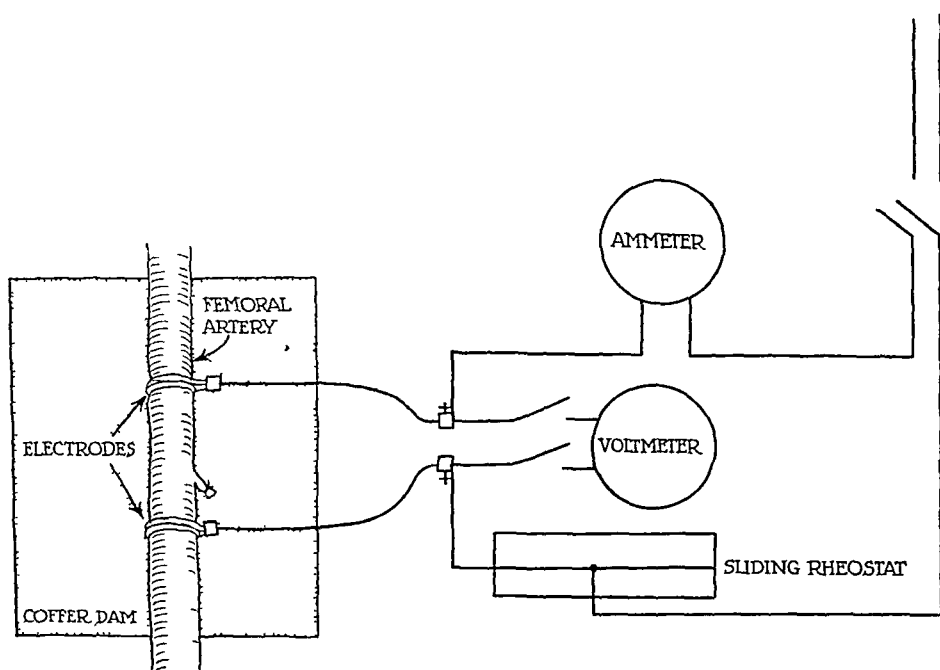


Fig 1—The set-up used in the experiments for the passage of the electric current through the femoral artery of a dog

loss of the current from passage around the electrodes through the body of the animal. The electrodes were connected with copper wires. The current was controlled by a sliding resistance of 3,000 ohms, and the intensity and tension were measured by an ammeter registering from 25 to 125 milliamperes and a voltmeter with a range of from 25 to 150 volts (see fig 1). Alternating currents of 110 and 220 and a direct current of 110 volts were used. The alternating and the direct current had the same effect. The currents were sent through the vessel for two minutes, four shocks, each of thirty seconds duration, usually being given. As soon as the current was closed, the muscles of the extremity were thrown into tetanic contractions, and, also, the portion of the vessel between the electrodes was contracted, the latter contraction persisting for from one to two minutes after the current had been broken. There was, however, a great variation in the intensity of the arterial contraction. In some of the experiments it was hardly visible, in others the vessel became almost colorless. An interesting

observation was the great fluctuation of the resistance of the vessel during the experiment, which often made the reading of the ammeter difficult. For reasons to be discussed later, it was deemed necessary to study the effect of the electric current when the circulation was interrupted. In these experiments, the artery was clamped at a point distal to the electrodes with a small clamp the branches of which were covered with rubber.

In order to determine whether anatomic changes might result from the mere handling of the vessel, we duplicated the experiments without applying the current.

After the experiment, the wound was closed by a double silk suture and covered with iodine collodum. The dogs were killed about a week later, and the vessels were fixed immediately with a 10 per cent solution of formaldehyde. A summary of the experiments is given in the table.

#### COMMENT

While in the first experiment the passage of the current through the artery had led to severe changes, lesions were not encountered in the

#### *A Summary of the Experiments That Were Made to Determine the Cause of the Severe Arterial Changes Seen in Burns Due to the Passage of an Electric Current*

No	Current Used,* Volts	Circulation	Amperage (MA)	Voltage	Duration, Minutes	Result
1	110 A C	?	30	—	2	Severe changes
2	110 A C	Free	30	—	2	No changes
3	110 A C	Free	35-50	—	2	No changes
4	110 A C	Free	50	26	2	No changes
5	110 A C	Free	50	65	2½	No changes
6	220 A C	Free	75	150	1½	No changes
7	110 A C	Stopped	55	80	1½	Severe changes
8	110 D C	Stopped	60	100	2	Severe changes
9	110 D C	Free	55	100	2	No changes
10	108 D C	Stopped	65	95	1½	Severe changes
11	108 D C	Free	65	90	2	No changes

\* A C means alternating current, D C, direct current

five experiments that followed, although they were conducted under apparently the same conditions. In an attempt to explain this striking difference of the results, it seemed most likely that in the first experiment the electrodes had been wound around the artery so tightly that the lumen had been unintentionally obstructed. With this point in view, the experiments were repeated and the circulation was interrupted at a point distal to the electrodes. Whenever the circulation was stopped during the passage of the current, severe damage was done to the vessel wall. Structural alterations, however, were not produced when the blood was circulating freely. These observations suggested that it was the heat liberated in the obstructed vessel that was detrimental to the tissues of the vascular wall. It was thought that the free circulation prevented the overheating of the wall, hence no ill effect was caused by the current.

In order to confirm this explanation we studied the effect of dry heat on the arterial wall. The femoral artery was prepared in the same



way as in the experiments with the electric current, and the surface was seared quickly with an aluminum steel wire, 3 mm in thickness, which had been heated over a Bunsen burner until it started to glow and which then had been allowed to cool for thirty seconds. Touching the vessel with the hot wire caused a marked constriction, which lasted for about one minute. A microscopic examination of this vessel a week later showed changes which resembled very much those observed in the experiments with the electric current and the compressed lumen, except that they were more severe.



Fig 2—The femoral artery, experiment 9, in which the blood was left flowing freely during the passage of the electric current. The vessel shows no changes. The thickness of the media and the appearance of the internal elastic membrane should be noted. (Frozen section stained with hemalum eosin,  $\times 80$ )

The lesions which were produced in the artery by the effective electric currents were as follows. Macroscopically, the exposed portion of the vessel was markedly distended and the wall was thin. It was so friable that often a slight handling with a forceps was sufficient to rupture it. Thrombosis was never observed, and in spite of the severe changes of the arterial wall circulatory disturbances did not appear in the extremity supplied by it.

Under the microscope, the media was the part of the arterial wall that was most severely affected. It was compressed and only half as thick as in the normal artery (the reader may compare figs 2 and 3). The nuclei of the muscle fibers of the media had disappeared as if they had been erased, and only a few shadow-like remnants were occasionally found near the internal elastic membrane (fig 3). In the hemalum-eosin stained sections, the media took a uniform pale purplish-gray color, in the van Gieson preparations, it appeared pale yellow with a few purple wavy lines. The elastic tissue was less severely changed. It stained well.

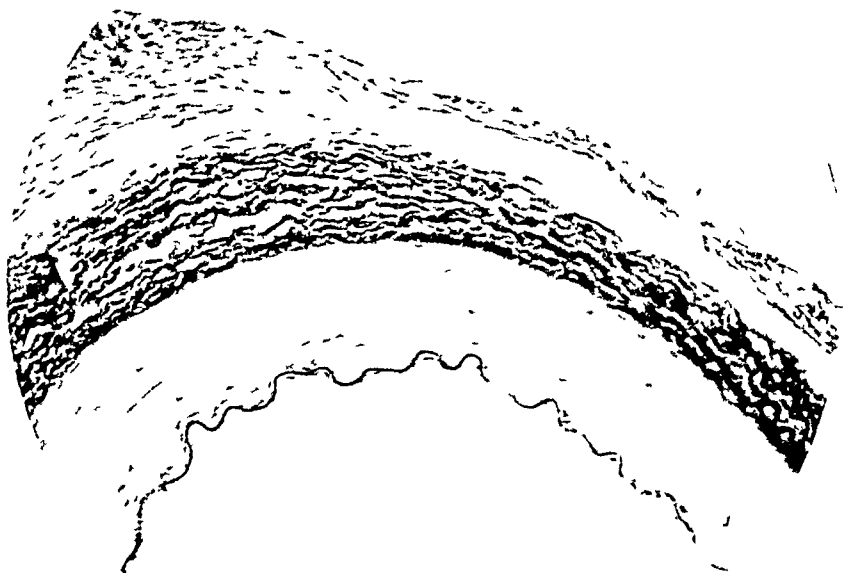


Fig 3—The artery, experiment 8, in which the flow of blood was stopped. The media is narrow and the lumen is wide. Pale-stained nuclear remnants are seen near the internal elastic membrane. Note the stretching of the internal elastic membrane. (Frozen section stained with hemalum eosin,  $\times 80$ .)

after Weigert, and in the media a system of branched and anastomosing fibers was seen, which differed from that of the normal artery only by the fibers being closer together. The internal elastic membrane, however, had lost its wavy appearance and was markedly stretched (fig 4). In one experiment, the membrane remained almost unstained in the sections stained after Weigert's elastica method. In this experiment, the endothelial lining was completely gone, while in the vessels with

less extensive changes the endothelial cells still were visible. They sometimes appeared swollen, bulging into the lumen with large hyperchromatic nuclei. The adventitia showed little change. The elastic fibers were stretched but stained well, and the nuclei of the collagenous tissue were normal.

Examining the region of the electrodes, one saw that the dead and the living tissue bordered on each other directly, and a line of demarcation did not form within the period of observation, which was one week. Piling up of lipid material about the necrotic zone as it is observed

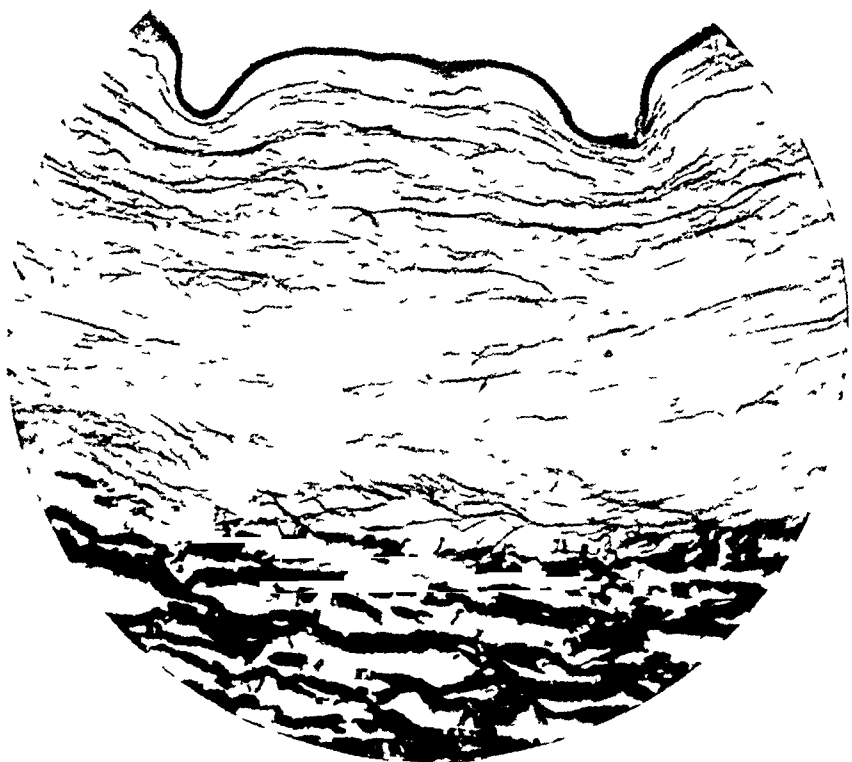


Fig 4—The artery, experiment 1. The internal elastic membrane is well stained but appears stretched. The media shows a network of elastic fibers, although the muscle fibers are gone. (Paraffin section prepared with Weigert's elastic stain and lithion carmine,  $\times 250$ .)

for instance, about anemic infarcts, was not seen. The necrosis did not stop in one level. In the outer third of the media, namely, it extended somewhat beyond the electrodes, and the borderline here ran circular (fig 5). In this region, the intima was thickened and the endothelial cells proliferated, forming a gland-like lining.

In the seared blood vessels, the changes were similar. The wall was thin and friable, and the muscle fibers of the media had been destroyed.

The elastic tissue was more severely affected than by the electric current. In many places, it did not take the specific stains. The adventitia, too, showed marked regressive changes. Where the wire did not touch the vessel, the wall was found intact, and there was not any demarcation between the living and the necrotic portion.

Figure 5 illustrates these observations. In the lower half of the picture, one sees the wavy internal elastic membrane. In the upper half where the media is necrotic, the elastic membrane is flattened, and at a point higher up not included in the photomicrograph, it has dis-

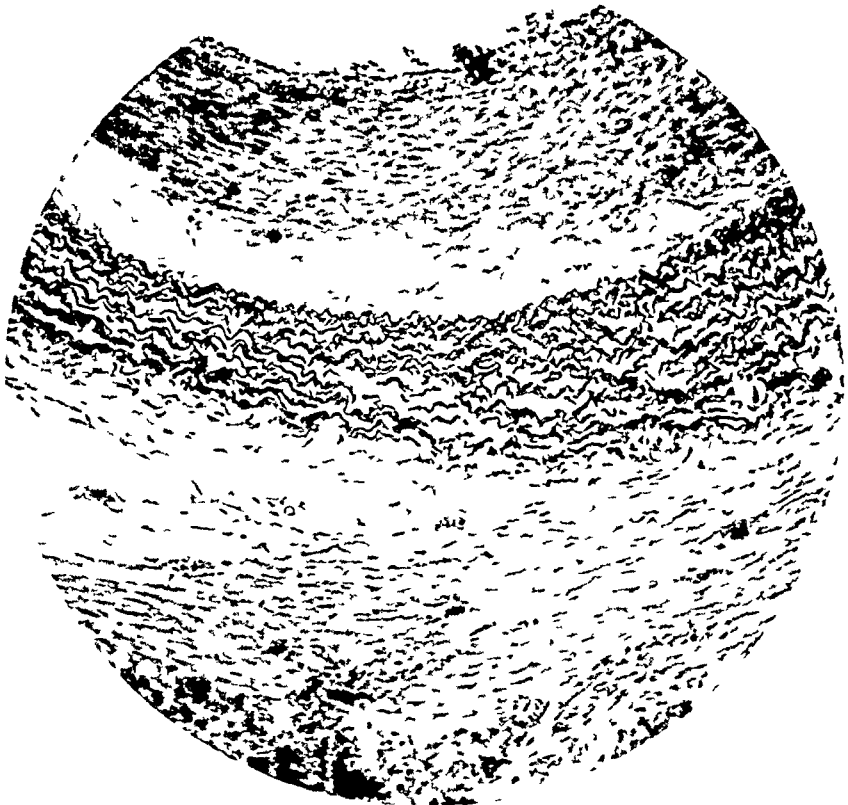


Fig 5—The artery, experiment 7, in which the circulation was stopped. This section is taken about 2 mm distal from the electrode. The outer portion of the media is necrotic, while the internal layer shows little change. There is a slight thickening of the intima and a marked proliferation of the endothelium. (Frozen section stained with hemalum eosin,  $\times 80$ )

appeared. In the media, a few elastic fibers can be made out. The intact portion of the elastic membrane is covered by an endothelial lining, the nuclei of which are distinct. Endothelial cells do not appear over the flattened portion.

It is evident from these observations that the differences between the lesions produced by the current and the lesions produced by the heat

were only gradual and that in places in which the action of the heat had been less intensive, as at the edges of the seared portion, the lesions were almost identical

#### SUMMARY

As in the lesions of the skin, the changes that were produced in the arteries by the electric currents were nonspecific. They were due to the heat and could be duplicated by a slight searing of the vessel with a hot wire. Low tension currents were effective when their action was combined with a compression of the lumen of the artery. This observation,



Fig 6—A section of a seared femoral artery. In the lowermost portion, the internal elastic membrane and the adjacent part of the media are not altered. Note how living and dead tissue border on each other without any line of demarcation. (Frozen section stained with hemalum eosin,  $\times 280$ )

too, indicated that it was the thermic injury which destroyed the highest developed structures of the wall. With a free circulation of the blood, the wall of the vessel was cooled and thus an excessive temperature was prevented. In accidents with high tension currents, this cooling apparently is not sufficient, and the wall is destroyed in spite of the circulating blood.

The muscle fibers of the media were the most sensitive part of the wall. The elastic tissue was more resistant, retaining its staining prop-

erties but losing its elasticity. This was indicated by the stretching of the elastic membranes. Extremely high temperatures caused a complete destruction of all the elements of the wall.

Deprived of the essential structures that secured the firmness of the wall, the vessel became dilated and a fusiform aneurysm was formed. Spontaneous rupture of the injured arteries was not observed. It is remarkable that the vessels could stand the blood pressure with the media practically gone. After the experiments, the exposed artery was covered by the fascia and the wound was closed by a double layer of silk sutures. This precaution, and the luxurious granulation tissue that formed within a short time after the experiment, apparently prevented the forcing of the blood through the arterial wall.

The adventitia showed a high resistance against thermal injuries. The elastic fibers were stretched, but the collagenous tissue was not affected. The endothelial lining of the intima was gone where the media and the internal elastic membrane were most severely damaged. In places of less severe changes, the endothelium sometimes showed proliferation. There was no thrombosis, the blood circulated freely through the dilated segment of the artery.

An interesting observation was the complete absence of defense reactions. The necrotic segment fitted into the vessel without interruption of the continuity. It seems as if the heat had destroyed those substances of perhaps enzyme-like nature that, in tissue necrotic from other causes (such as lack of nutrition or toxins) stimulate its demarcation.

In a later publication, the final outcome of these vascular changes will be described.

#### CONCLUSION

The severe arterial changes that are frequently found in the vicinity of electric burns are due to the heat and are nonspecific for the action of the electric current.

# AORTIC LESIONS IN DOGS CAUSED BY INFECTION WITH SPIROCERCA SANGUINOLENTA \*

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NEW ORLEANS

Experimental Infection of Dogs with the Larvae

Macroscopic examination

Microscopic examination

General considerations

Natural Infection of Dogs with Spirocerca

Macroscopic examination

Microscopic examination

General considerations

Comment

Conclusions

In 1922, one of us (Faust) found that the Asiatic hedgehog, *Eumeces dealbatus*, taken in the vicinity of Peking, was infested with large numbers of larval nematodes, identified on morphologic grounds by Schwartz,<sup>1</sup> in 1926, as *Spirocerca sanguinolenta*. These larvae were encysted in the tissues of the omentum and mesentery and on the peritoneal wall of the stomach and duodenum. During 1926 and 1927, Faust<sup>2</sup> fed these encysted larvae to dogs, cats and rabbits in an attempt to corroborate the morphologic diagnosis of the worm and to trace the route of migration through the tissues of the definitive host. The results showed clearly (1) that the dog was the natural mammalian host, although the early stages in the route of migration might be equally well observed in the cat, and (2) that the larvae after excystment in the stomach passed directly through the gastro-epiploic veins into the portal blood stream and thence by way of the capillaries of the liver and the lungs to the aorta, to which the worms became attached and in which they produced significant lesions.

The present paper embodies a study of the microscopic changes associated with these aortic lesions, undertaken with a view to determining

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1 Schwartz, B. Parasitic Nematodes from China, Proc U S Nat Mus 68 1, 1926

2 Faust, E C. Migration Route of *Spirocerca Sanguinolenta* in Its Definitive Host. Proc Soc Exper Biol & Med 25 192, 1927

the extent of the lesions and the course of migration of the worms through the aortic wall. In all, a series of fifteen dogs was used, of which seven were infected experimentally and the others naturally.

### EXPERIMENTAL INFECTION WITH THE LARVAE OF *SPIROCERCA SANGUINOLENTA* IN DOGS

The puppies used for the series of experimental infections were born and reared in the laboratory. The technic employed in the work was similar to that described in a previous communication<sup>2</sup>. The period of incubation extended from four to thirty days.

### MACROSCOPIC EXAMINATION

CASE 1—The period of incubation was four days. The intima of the aorta from the arch to the seventh intercostal arteries was normal. From the latter level to the tenth intercostal arteries, just above the origin of the celiac axis, there were several worms attached to or embedded in the aortic wall, and lineal hemorrhages could be seen (fig. 1). Some of the worms lay partially free in the aortic lumen, but others were entirely buried in the aortic wall, just under the internal layer. The intima took on serpiginous elevations corresponding to the embedded worms. Furthermore, there were worms still free in the aortic lumen. The celiac artery showed similar lesions, but the mesenteric artery was not modified.

CASE 2—The period of incubation was five days. The lineal hemorrhages were spread along the aortic intima from the fourth intercostal arteries to the celiac artery, and were more marked in the lower portion of the vessel (fig. 2). Several worms were found free in the aortic lumen, but more frequently they were attached to or buried in the aortic wall. The celiac artery showed similar changes, but the mesenteric artery was only slightly affected. The changes at this stage were similar to but more intensive than those in the earlier stage.

CASE 3—The period of incubation was seven days. In the intima of the aorta, from its origin to the celiac artery, there were two types of changes, one of which consisted of the formation of nodules, the other of small dotlike hemorrhagic depressions. The nodules were arranged longitudinally, within 1 cm. of each other. The uppermost one was situated about 1 cm. from the common carotid artery. These nodules were each a little bigger than a pea, and in the natural state were whitish gray. The hemorrhagic depressions were usually scattered throughout the wall, between the fourth and seventh intercostal arteries. Many worms were attached to the lower part of the thoracic aorta and the upper part of the abdominal aorta.

CASE 4—The period of incubation was eleven days. The aortic wall had a rough appearance throughout, from the posterior termination of the arch to the origin of the celiac artery (fig. 3). Many worms were buried in the aortic wall, only a few were free in the lumen. Hemorrhagic dots and lines were numerous. On the cut surface of the thickened media there were several small white dots within hemorrhagic areas.

The adventitia adhered to the surrounding tissue and showed a marked diffuse hemorrhage with numerous small white dots. The lesions along the thoracic aorta were somewhat more severe than those along the abdominal aorta. The celiac artery showed almost the same degree of modification, but the lesions on the mesenteric artery were less extensive.





Figure 1

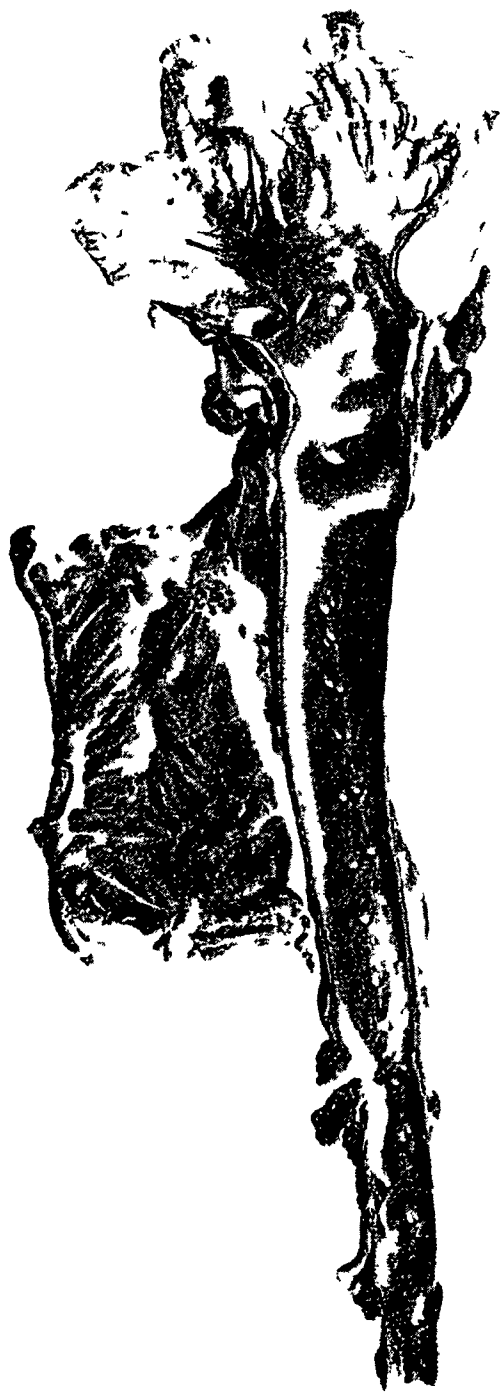


Figure 2

Fig 1—The aorta of a puppy four days after the latter had been fed encysted third-stage larvae of *Spirocerca sanguinolenta*. The hemorrhagic linear tracts in the region of the abdominal aorta should be noted, natural size

Fig 2—The aorta of a puppy five days after an experimental infection with the larvae of *Spirocerca sanguinolenta*. Linear hemorrhages in the region of the abdominal and posterior part of the aorta are to be noted, two-thirds natural size



Figure 3

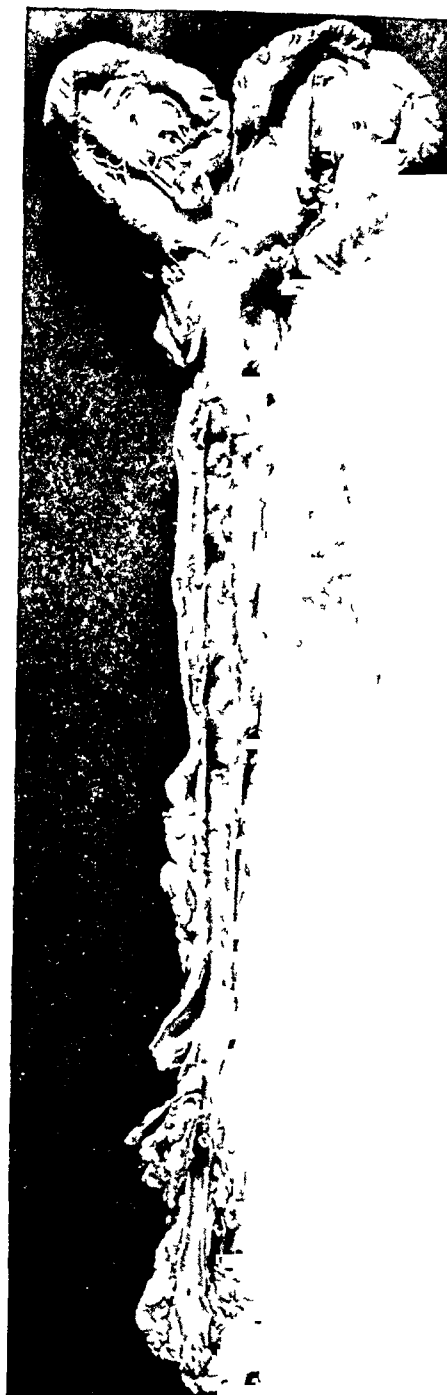


Figure 4

Fig 3—The aorta of a puppy eleven days after an experimental infection with the larvae of *Spirocerca sanguinolenta*. Panarteritis purulenta is seen extending as far forward as the arch, two-thirds natural size

Fig 4—The aorta of a puppy thirty days after an experimental infection with the larvae of *Spirocerca sanguinolenta*. Tremendous fibrosis and the formation of nodules and aneurisms may be seen in the thoracic aorta, and a more or less normal appearance of the abdominal aorta, two-thirds natural size

CASE 5—The period of incubation was thirteen days. The aorta, from the posterior part of the arch to the commencement of the celiac artery, showed marked changes. The lesions were particularly prominent in the thoracic portion of the aorta. The inner aspect of this region appeared rough and irregular owing to numerous small elevations. Many of these were accompanied by hemorrhage. Moreover, in this region there were many blood-colored worms buried in the aortic wall. The corresponding adventitia adhered to the surrounding tissue and was invaded by many small white nodules and hemorrhagic areas. The abdominal portion of the aorta presented only a rough appearance, with numerous dotlike depressions over it.

CASE 6—The period of incubation was fourteen days. The aorta throughout, from its origin in the thoracic region to the commencement of the celiac artery, was rough, owing to irregular thickenings, gross nodules, however, were not seen. The lesions were more severe in the thoracic portion of the aorta than at other levels. Worms were also found attached to and buried in the tissues.

CASE 7—The period of incubation was thirty days. The aorta, from the posterior part of the arch to the commencement of the seventh intercostal arteries, was thickened as a whole (fig 4). Throughout this region there were numerous small nodules, some of which were fused with their neighbors. The inner aspect of this portion of the vessel was extremely rough and irregular. The adventitia corresponding to this part adhered firmly to the surrounding tissue. In the cut surface of this tissue, worms were found that were apparently alive. Besides the thickening, small dotlike depressions without hemorrhage were seen throughout the aortic intima.

#### MICROSCOPIC EXAMINATION

CASE 1—After an incubation of the larvae for four days, a section from the abdominal aorta, to which the worms were attached, was examined. The whole tissue was normal, except where the worms were embedded in the superficial layer of the media. Hemorrhage was not found in the immediate vicinity of the worms, but several small hemorrhagic foci were observed in places in which worms might have been previously situated. There was neither destruction of the media nor hemorrhage in the adventitia.

CASE 2—After an incubation of the larvae for five days, a section from the abdominal aorta, in which the worms were embedded (fig 5), was examined. Except for the worms embedded in the media, the tissues did not show changes. Some of the worms were lodged in the superficial layers of the media, others in the deeper layers. Hemorrhages were not seen around the worms, although small hemorrhagic areas were present in foci in which worms did not appear. In the adventitia there was an infiltration of many eosinophilic polymorphonuclear cells without hemorrhage.

CASE 3—After an incubation of the larvae for seven days, a section from a nodule of the aorta was placed under the microscope. Except for the nodular part, it did not show any thickening of the intima. The nodule consisted of dense fibrous tissue, without elastic or muscle fibers. In the deeper part of the plaques, there were small capillaries, some of them containing red corpuscles. The most marked change was in the media. Just under the intimal plaques, the media was markedly destroyed, owing to fibroblastic growths. These fibroblasts were also seen in certain other areas. Some of them had broad connections with the adventitial connective tissue. The lamellar elastic fibers disappeared in the areas in which the fibroblastic growths were present. Therefore, the most marked

reduction in the elastic fibers was seen in the part just under the intimal plaques. In the fibroblastic growths, small capillaries were commonly present. Cellular infiltration was not particularly evident. The adventitial layer was without remarkable changes, except for an infiltration with eosinophilic polymorphonuclears and round cells, and a slight hemorrhage.

A section from the hepatic artery, in the wall of which the worms were embedded, was examined. Thickening or other change was not present in the intima. In the vicinity of the worms there was not any marked reaction in the media, but along the canal through which the worms had entered the tissue there were many wandering cells and round cells. There were some small areas

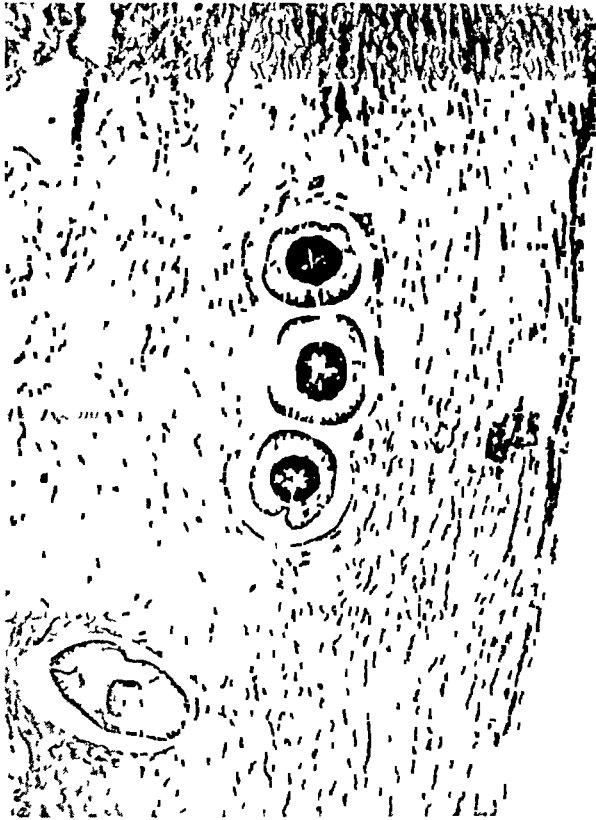


Fig 5—A section through the abdominal aorta of a puppy five days after an experimental infection with the larvae of *Spirocerca sanguinolenta*. The worms may be seen embedded in the media. There are no marked changes in the tissues,  $\times 100$ .

in which the muscle fibers were necrotic and infiltrated with wandering cells and round cells. Infiltration with eosinophilic polymorphonuclear cells was common. The cellular infiltration was marked in the adventitia. Among these cells, eosinophils were the most numerous, hemorrhages were common.

CASE 4—After an incubation of the larvae for eleven days, a section from the thoracic aorta (fig 6) was examined. The intima was not thickened. The media was infiltrated with large numbers of eosinophils. In some regions, these cells were grouped together in local foci, in others, they were diffusely scattered throughout the media. In addition to the cellular infiltration, diffuse hemorrhage

was present. In the part adjacent to the adventitia, there were small newly formed capillaries derived from the adventitial layer. The formation of fibroblasts and small capillaries was marked in this layer, which was thickened throughout and hemorrhagic.

CASE 5—After an incubation of the larvae for thirteen days, the aortic intima was edematous. Many polymorphonuclears and round cells were present. The former had infiltrated the media both in local foci and diffusely throughout the layers. Granulation tissue had developed markedly, having connection with the adventitia. Hemorrhages and worms were also found in the media. The adventitia was conspicuously infiltrated with polymorphonuclear cells. It showed a growth of granulation tissue.

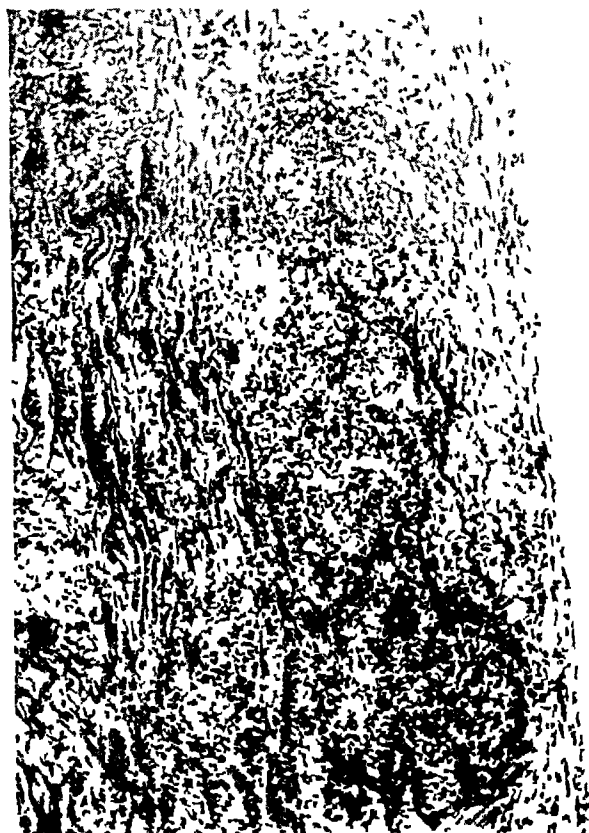


FIG 6—A section through the thoracic aorta of a puppy eleven days after an experimental infection with the larvae of *Spirocerca sanguinolenta*. Cellular infiltration and diffuse hemorrhage in the media and fibrosis of the adventitia are to be noted,  $\times 100$ .

CASE 6—After an incubation of the larvae for fourteen days, a section from the upper part of the thoracic aorta (fig 7) was examined. The intima was slightly thickened, through the growth of dense fibrous layers. Corresponding to the marked destruction of the media, the intima was moderately thickened. Owing to the irregular growths of fibroblasts, the media was conspicuously destroyed, so that the normal arrangement of the media could scarcely be found, particularly of the part around embedded worms. On the other hand, the necrotic areas were infiltrated with polymorphonuclears, round cells and wandering cells. The destruction and resorption of the lamellar elastic fibers were

so complete that this portion of the media was hardly recognizable, and the boundary between the media and the adventitia was frequently obliterated

There was marked cellular infiltration in the adventitia. The eosinophilic polymorphonuclear cells were the most abundant. Histiocytes and round cells were also present. Hemorrhage was common throughout the layer.

CASE 7—After an incubation of the larvae for thirty days, a section from the upper part of the thoracic aorta was examined. The nodule consisted of dense fibrous layers and some muscle and elastic fibers in place of the normal intima. The myo-elastic layer appeared only inconspicuously in the deepest



Fig 7—A section through the upper part of the thoracic aorta of a puppy fourteen days after an infection with the larvae of *Spirocerca sanguinolenta*. Profound destruction and absorption of elastic and muscle fibers, leukocytic infiltration, diffuse hemorrhage and irregular fibroblastic replacement are seen,  $\times 100$ . Elastic-fiber staining.

portion of the nodule. The region of the media was noticeably thickened, while the normal tissues were profoundly altered. Fibroblastic areas, including small capillaries, as well as necrotic foci, were seen. Dead worms and small hemorrhagic lakes were also found. Cellular infiltration was fairly apparent throughout the entire media, eosinophils and round cells were common. The destruction and resorption of the lamellar elastic fibers were almost complete. The adventitia

was also conspicuously thickened. Fibroblastic growths were evident. Cellular infiltration was tremendous, the polymorphonuclear cells being the most abundant, and siderophilous cells numerous.

#### GENERAL CONSIDERATIONS

The aortic lesions were different in nature, in intensity and in localization, according to the length of the period of incubation. The experimental infection could be divided into three stages: the first, represented by the observations at four, five and seven days; the second, by those at eleven, thirteen and fourteen days; and the third by those at thirty days. The lesions consisted of hemorrhage, purulent inflammation and hypertrophy.

In the first stage, we saw only the worms embedded in the aortic wall, the areas of small localized hemorrhages that had occurred after the invasion of the worms and the infiltration of the adventitia with eosinophilic cells. The worms could be found only in the media, having more deeply invaded this layer in the five days' incubation than in the four days' incubation. Hemorrhage was present in the adventitia. The hemorrhage was lineal, and could be seen from the inner aspect only as a serpiginous line, as if it were a red-colored tracing on ivory. Later, it became diffused throughout the media and the adventitia, so that these coats were stained red. The lesions in the first stage (particularly at from four to five days after infection of the puppies) were localized mainly in the abdominal aorta near or anterior to the origin of the celiac axis, which was itself involved in the change.

Corresponding to the progress in the time of incubation, the lesions became more complicated and gradually extended toward the thoracic aorta. In the second and third stages, in contrast with the first stage, the significant lesions were situated at the thoracic level of the aorta. The most remarkable lesions in the second and third stages were the purulent inflammation and the hemorrhages in the media and the adventitia. The former occurred in both the diffuse and the localized types. The small white dots, which were observed macroscopically, were not other than foci of purulent inflammation. The localization and the size of these pustules were variable. But usually large purulent areas were not seen immediately beneath the endothelial layer. Hemorrhages of a rather diffuse type commonly occurred. In the adventitia, the granulation tissue consisted of fibroblasts and newly formed capillaries. These tissues were on the point of entering the media. Besides the growth of the granulation tissue numerous eosinophils and hemorrhages were seen.

The lesions that have been described constitute a panarteritis purulenta. It is interesting to note, moreover, that this process was not found developing in the region in which the lesions of the first stage were most common: that is, in the abdominal aorta. The purulent

inflammation described was peculiar and different from that observed in cases of the infection in man in that the infiltrated cells were mainly eosinophilic polymorphonuclear leukocytes

In the third stage, the purulent foci had already been resorbed. Instead of pus pockets, there was localized granulation tissue. In these areas, the elastic and muscle fibers, for the most part, were destroyed and resorbed. The intima became thickened in the region corresponding to the destroyed media. The hemorrhage in the aortic wall had disappeared, but siderophilous cells were numerous in the adventitia.

It is now necessary to consider the way in which the worms invade and progress through the aortic wall. The larvae, once within the systemic circulation, gained entrance to the region of the thoracic and the upper part of the abdominal levels, we never found the lesions on the arch, the anteriorly directed arteries or the lower part of the abdominal aorta behind the celiac axis. Yet, in spite of the common presence of worms attached to the abdominal aorta in the early stage, the characteristic lesions, combined with the presence of the worms, were later found only on the thoracic aorta. If the worms that invaded the abdominal aorta penetrated outward, then there should have been adventitial hemorrhage and other profound reactionary lesions in this portion of the vessel. Such hemorrhages and inflammatory foci were not commonly found in the media of the abdominal aorta. For these reasons, we believe that the worms which entered the intima of the abdominal aorta soon migrated anteriorward toward the thoracic aorta, advancing within the middle coat. In support of this hypothesis is the arrangement of small dotlike depressions, which were more evident in the later stage when they were covered with an endothelial layer. The arrangement of these depressions was peculiar, that is, lineal and longitudinal to the aortic axis. It is altogether unlikely that the depressions indicated the points of entrance of part of the worms, since they were not combined with endothelial failure and hemorrhage. We suggest that these depressions may have been produced after the failure of the tissue of the superficial medial coat, caused by the advancing of the worms.

The further migration of the worms from the media to other layers is also an important point of investigation. We saw the worms embedded in the thickened adventitia during the second or third stage, but never during the first stage. Likewise, in the adventitia, in the second stage, purulent foci and hemorrhage were found, which without doubt were due to the worms rather than to micro-organisms for we never saw purulent inflammation on the abdominal aorta. Some by-product of the worms was presumably responsible for this inflammatory process. Thus, we believe that the pus patches indicated former foci of the worms.



In spite of the fact that some of the worms embedded in the aortic wall undoubtedly died in situ (we saw the worm dead in the media during the third stage), we have substantial proof that the majority of the worms migrated out of the thoracic aorta during the second stage. From the facts mentioned, we may conclude that the penetration of the worms through the adventitia is certain.

#### NATURAL INFECTIONS WITH *SPIROCERCA* *SANGUINOLENTA* IN DOGS

In this study, eight dogs that were naturally infected with *Spirocerca* were examined. With the exception of one dog, which had been secured in Peking, all the others had been examined post mortem by one of us (Faust) in Amoy. The periods of incubation of the worms in these dogs were undoubtedly longer than the periods in the experimental cases. The dogs with the natural infections provided material that was particularly helpful in the study of lesions that had arisen from prolonged incubation.

#### MACROSCOPIC EXAMINATION

CASE 1—With the exception of a few small dotlike depressions, the aortic arch did not show changes. On the thoracic aorta there were four depressed patches and one small nodule. One of these patches was deep and was the size of a pea, the others were shallow and narrowly elliptic. The margins of these latter depressions were whitish gray and were slightly elevated. On the abdominal aorta, a few small dotlike depressions were found.

CASE 2—The changes in this case were relatively simple, that is, two nodules and numerous small dotlike depressions. The two nodules were situated on the thoracic aorta. One of these measured about 10 mm in diameter. The other was smaller, being about 7 mm in diameter. Both nodules were whitish gray. The small dotlike depressions were distributed in considerable numbers from the upper part of the thoracic aorta to the abdominal aorta.

CASE 3—On the thoracic aorta and the upper part of the abdominal aorta several small nodules and depressed patches were noted. These depressions were each about the size of a rice grain. The small dotlike depressions were numerous and were distributed throughout the thoracic and the abdominal aorta.

CASE 4 (fig 8)—The thoracic aorta was profoundly modified, showing a closely arranged pattern of many depressions, each about 10 mm in diameter. The aortic wall at this level was distended and much thinner than it was in the other parts. Besides the larger depressions, a few elevated patches were seen along the vessel.

CASE 5—On the lower part of the thoracic aorta there were three depressed patches. Two of them were shallow and were each about the size of a pea. The other was bigger, being the size of a broad-bean, and had a deep thin wall. Small dotlike depressions were distributed along the lower part of the thoracic aorta and the upper part of the abdominal aorta.



Fig 8—The thoracic aorta and the adjacent portion of the esophagus of a dog that has been naturally infected with *Spirocera sanguinolenta*. The nodules and the aneurisms in the wall of the aorta and the large nodules in the esophageal wall are to be noted. The adult worms live in the latter nodules, natural size.

CASE 6—On the lower part of the thoracic aorta there were three depressions, each about the size of a pea. Small dotlike depressions were numerous on the lower part of the thoracic aorta and the upper part of the abdominal aorta.

CASE 7 (fig 9)—The lesions in this case were marked throughout the entire thoracic aorta. Adjacent to the arch there were several small depressions. Their margins were slightly thickened. From this region to the sixth intercostal arteries, there were several small depressions. The inner aspect of this region had an



Fig 9—The thoracic aorta of a dog that has been naturally infected with *Spirocerca sanguinolenta*. It shows the formation of nodules and aneurisms and an adjacent uninfested portion of the esophagus, natural size.

extremely irregular appearance. Besides these depressions, one nodule was seen on the upper part of the thoracic aorta, with a diameter of about 10 mm. Small dotlike depressions were commonly distributed throughout the wall of the vessel.

CASE 8—On the lower part of the thoracic aorta and the upper part of the abdominal aorta, there were marked changes consisting of closely arranged nodules and large and small dotlike depressions. However, these nodules and depressions were all rather small as compared with those observed in the other members of the series. The inner aspect of the wall appeared rough and irregular.

## MICROSCOPIC EXAMINATION

CASE 1—A section from the aneurismic cavity was examined. The boundary between the intima and the media could not be seen. The elastic fibers were almost completely resorbed, and had been replaced by dense lamellate fibrotic layers. Although muscle fibers were to be seen more commonly toward the inner surface than on the outer side, there was a marked reduction from the normal number. In the adventitia, we saw numerous siderophilous cells. Cellular infiltration was not evident.

CASE 2—Sections from a nodular portion were examined. A boundary between the intima and the media, in the part corresponding to the most elevated



Fig. 10—A section from an aneurismic cavity of the thoracic aorta of a naturally infected dog (case 4), showing enormous thickening, the destruction of elastic and muscular fibers, and their replacement by dense fibrotic and fibroblastic growths,  $\times 43$

part of the nodule, could not be found. This part consisted mostly of dense fibrotic layers without any elastic and muscle fibers. In certain regions, the dense fibrotic layers had a tissue connection with the adventitial fibrotic layers. In the depth of the nodule, we saw a marked localized cellular infiltration. Among the infiltrated cells, the histiocytes and fibroblasts were the most numerous, although small round cells and polymorphonuclear cells were also numerous.

The intima adjacent to the nodule was slightly thickened, and consisted of elastic and muscle fibers. In the media of these parts, dense fibrotic layers arose continuously from the nodular area. Siderophilous cells were commonly observed in the adventitia.

CASE 3—Sections from the slit-shaped depressions were examined. The intima was moderately thickened, owing to the growth of the elastic, muscular and fibrotic tissues in areas in which the media showed more or less marked lesions. Around the margin of the depression, the media was destroyed by dense fibrotic and fibroblastic growths, so that we did not see elastic and muscle fibers in this region. The other parts of the media did not indicate any marked change. Cellular infiltration was seen only in the fibroblastic layer. Siderophilous cells were also present in the adventitia.

CASE 4—Serial sections from the aneurismic cavity (fig 10) were examined. The intima was enormously thickened. In the corresponding media, traces of the ordinary structure of the media were not found. This region consisted, as a whole, of dense fibrotic and fibroblastic growths. The outermost layer of this thickening seemed to be compressed from the inside and showed a firm appearance.

Adjacent to this cavity there was neither thickening of the intima nor modification of the media. The margin of the cavity was elevated slightly throughout the fibrotic layer. Worms could not be found. Siderophilous cells were present in the adventitia.

CASE 5—Sections from the large aneurismic cavity were examined. The intima was moderately thickened, owing to the growth of fibrotic and muscle elements mingled with small amounts of elastic fibers. At the bottom of the cavity, the boundary between the media and the intima had disappeared, and a large amount of bone with bone-marrow was to be seen. The dense fibrotic layers had grown measurably at the expense of the elastic and muscle fibers. Where the media did not show lesions, the intima was not modified. There were extremely few siderophilous cells in the adventitia. Infiltration of this layer with cells was not observed.

CASE 6—Sections from the aneurismic cavity were examined. The boundary between the intima and the media was obscured. This region consisted mainly of a dense fibrotic layer, containing bone tissue with bone-marrow. Elastic and muscle fibers were not seen. Round cells were moderately common, and small capillaries were visible. Owing to fibrotic growth, there was thickening of the intima adjacent to the margin of the cavity. In the adventitia, there were numerous siderophilous cells.

CASE 7—Serial sections from the nodular portion (fig 11) were examined. The nodule consisted of densely fibrosed layers of intima. The boundary between the intima and the media in the nodular part was already obscure, and the corresponding part of the media consisted of fibrotic or fibroblastic growths instead of muscle and elastic fibers. The dense fibrotic tissue in some areas had changed into hyaline or cartilaginous tissue, furthermore, we saw bone tissue in the depth of the nodule.

Adjacent to the nodule, the intima was thickened more or less, through fibrotic or fibroblastic growths. Not far from the nodule, however, no thickening was present. The lesions in the media corresponded in position rather closely with the intimal thickening, that is, the most marked lesions were seen where the intima was most noticeably thickened. Small capillaries were seen everywhere throughout the whole of the media, but cellular infiltration was not noticeable. Siderophilous cells were found in the adventitia.

Worms could not be found in any of the sections.

Serial sections from the small slit-shaped depression were examined. The intima was thickened throughout by dense fibrotic and fibroblastic growths. The inner surfaces of this depressed intimal thickening showed marked irregu-

larities The boundary between the intima and the media was not visible The margin of the depression was slightly elevated

Worms were not found anywhere in the sections Siderophilous cells were present in the adventitia

CASE 8—Sections from the shallow depression were examined The intima was slightly thickened The media of this region consisted of dense fibrotic and fibroblastic growths, and was thickened to about twice its normal size This medial thickening extended mostly outward In the adventitia and the surrounding tissue, many siderophilous cells were seen



Fig 11—A section through a nodular portion of the thoracic aorta of a naturally infected dog (case 7), showing formation of bone,  $\times 100$

#### GENERAL CONSIDERATIONS

The lesions in the cases of natural infection could be divided into three main groups small dotlike depressions, nodules and depressed “holes” The depressed “holes” were really small localized aneurisms, the depressions having been produced by the expansion of the aortic wall at a particular location These small aneurisms, of course, did not occupy the entire circumference of the aortic wall, and each usually constituted only a saccular diverticulum But if these aneurisms in large

numbers were situated close to one another, then the aortic wall expanded as a whole. A good example of this was found in case 4.

The small aneurisms could be divided into two types. One was slit-shaped, the other looked as if it had been produced by pressure of the finger. Some of the slit-shaped depressions had consistently thickened margins, but others did not. The thickened margin appeared similar to that of the nodule. The other type of aneurism did not have a thickened margin, it consisted only of a diverticular sac of the aortic wall, the thinness of the wall being indirectly proportional to the size of the sac.

The nodules were whitish gray and never yellowish. The smallest nodule was the size of a white bean, the largest about that of a broad-bean. Their consistency was always hard. With the exception of those in case 8, the aneurisms and the nodules were found consistently on the thoracic aorta. The small dotlike depressions were distributed throughout the thoracic and the abdominal aorta, arranged somewhat in a linear pattern. It is interesting that the small depressions could be seen commonly on the abdominal aorta, particularly on the portion adjacent to the celiac axis, although on this part the nodules and the aneurisms were never seen. The lesions were situated, for the most part, on the back wall of the aorta.

The most marked change in this series was the destruction of the media. In both the nodular and the aneurismic portions, the media was destroyed in the same manner, namely, by the resorption and replacement of muscle and elastic fibers. Instead of these fibers there were growths of dense fibrotic and fibroblastic tissue. We never saw the boundary between the intima and the media in these parts. The amount of intimal thickening could be easily appreciated by comparison with the adjacent normal intima, even though the boundary between the intima and the media was indefinite. Thickening of the intima was not seen except in those regions in which there was destruction of the media. The fibrotic and fibroblastic growths usually broke out in localized patches.

These growths developed somewhat differently on the nodule and in the aneurismic cavity. In the region of the nodule, they produced a thickening of the media, in the aneurismic cavity, they became denser and rather decreased in thickness. Small capillaries and cellular infiltration were always found in the media, although at times they were not conspicuous. Besides these lesions, we saw osteoblasts in the media, some of them even had bone-marrow. The adventitia was usually thickened, more or less, by means of fibrotic growths. We did not find hemorrhage, but always found numerous siderophilous cells. In spite of careful examination through the several sections, we could not find traces of worms in any part of the aortic wall.

It is desirable at this point to compare the nodular type with the aneurysmic type of lesion. For convenience, their relative frequency in this series is set down in the accompanying table.

These cases may be naturally divided into three groups: (1) those in which there was building of the nodule, without aneurysmic cavities (case 2), (2) those in which there was building of aneurysmic cavities without nodules (cases 3, 4, 5 and 6), and (3) those in which there was building of both nodules and aneurysmic cavities (cases 1, 2, 7 and 8).

As previously mentioned, the histologic changes represented in the nodular and aneurysmic lesions were similar, with this difference, that

*Comparative Frequency of Nodules, Aneurysmic Cavities and Dotlike Depressions in Cases of Natural Infections with Spirocerca in Dogs*

Case	Nodule	Aneurysmic Cavities	Dotlike Depressions
1	One, small	Four, one of which was the size of a pea, the others, small and shallow	Common
2	Two, one of which was the size of a small finger tip, another, the size of a bean	None	Very common
3	None	Several, slit shaped, not large and deep	Very common
4	None	Many, each the size of a small finger tip	Common
5	None	Three, the largest the size of a broad bean, and the others, each the size of a pea	Very common
6	None	Three, each little bigger than a pea	Very common
7	Several one of which was the size of a small finger tip, the others, all small	Several small and shallow, slit-shaped	Very common
8	Several the largest of which was the size of a bean	Two, small and shallow	Very common

the fibrotic layer of the aneurysmic media was denser. It seems probable that the aneurysmic cavity replaced the nodule. We called attention to the slit-shaped depressions with thickened margins. These constituted an intermediate stage between the nodule and the aneurysmic diverticulum. Accordingly, the case which had an aneurysmic cavity was older than the case which had the nodule alone. Thus, we may conclude that the period of incubation was shortest in the first group, and longest in the second group, while in the third it was intermediate. With few exceptions, these lesions were always situated on the thoracic aorta.

Although worms were not seen in these lesions and although the formation of giant cells was not observed, siderophilous cells, which were commonly present in the adventitia, were indicative of previous hemorrhage in that issue. For these reasons, we may conclude that the worms that caused the aortic lesions had already penetrated the aortic wall.



## COMMENT

As far as we are aware, the aortic lesions produced by *Spinoerca sanguinolenta* in the dog are not duplicated by any other infection in this host. Comparable infestations with nematodes in water buffaloes and in cattle in the Dutch East Indies and in Annam (*Filaria poeli* Vityburg, 1897), and those in cattle in Annam and Senegal (*Onchocerca armillata* Railliet and Henry, 1909) produced almost identical lesions, with hypertrophy of the intima, dissociation of the elastic fibers, and destruction of the muscular elements with formation of osteoblasts, but without as marked changes in the adventitia—the gross picture being that of a formation of nodules leading to the development of aneurisms along the wall of the aorta (Bernard and Bauche,<sup>3</sup> Commes and Devanille<sup>4</sup>). Essentially similar changes were produced in the ileoceocolic artery in horses by species of the nematode genus *Sclerostoma* (Adelmann<sup>5</sup>). In all these infections, the adult worms were found in the wall of the digestive tract at a level corresponding to the level of the aortic lesions.

In bovine and equine species, the pathologic processes have been studied only after the worms have migrated out of the arterial wall and have become lodged in the wall of the digestive tract. The earlier stages of this type of verminous infection, including the method of attachment to and invasion of the aortic wall, the passage of the worms into the media and the concomitant changes of the tissues involved, are here described for the first time. It seems altogether likely, however, that a similar course is pursued by the nematode parasites producing aortic lesions in cattle and horses.

Atheromas of the aorta in man, leading to the formation of aneurisms are, for the most part, syphilitic in origin. While the gross alterations of the aorta are similar to those produced by *Spiroerca sanguinolenta* in dogs, the presence of granulation tissue (gummas) and giant cells, and the absence of eosinophils and of osteoblasts, as well as the usually demonstrable presence of the organism *Spirocheta pallida* in the tissues, all serve to distinguish these two types of lesions. Syphilitic aneurism also occurs higher on the arch than does verminous aneurism.

A perforation of the weakened dilated portions of the aortic wall was not recorded for any of the members of the experimental series reported in this paper. However, in an earlier series, which was used for tracing the route of migration of the larvae of *Spinoerca* from the lumen of the stomach to the aortic wall (Faust<sup>2</sup>), death of one host

3 Bernard, P. N., and Bauche, J. Filariose et atherome aortique du buffle et du boeuf, Bull. Soc. de path. exot. **5** 109, 1912.

4 Commes, Charles, and Devanille, P. L'onchocercose aortique bovine dans le Haut-Senegal-Niger, Bull. Soc. de path. exot. **10** 459, 1917.

5 Adelmann, F. Das Aneurysma verminosum equi, Berlin, L. Schumacher, 1908.

from perforation of the aorta just behind the arch occurred fourteen days after the feeding of the cysts, the perforation most probably being caused by the actively penetrating advanced third-stage larva that was found attached to the adventitia near the point of perforation. Other animals on which autopsies were made at from nine to thirty days following infection, had lesions so deep that only a thin layer of the adventitia remained unperforated. In general, it was noted that this more rapid acute termination of the infection resulted when the larvae were more mature and consequently larger at the time that they were fed to the host. Likewise, the delicate aortic wall of puppies was more likely to be perforated rapidly than was the thicker one of the adult dog. Perforation in the case of advanced chronic lesions in naturally infected animals due to gradual weakening of the wall at the site of the formation of a nodule or of an aneurysm also occurred not infrequently and resulted in fatal hemorrhage.

#### CONCLUSIONS

The mature third-stage larvae of *Spinocerca sanguinolenta* can be found in the aortic wall for the first time about four days after the feeding of cysts. The majority of the worms are found at about the twelfth or the thirteenth day.

The larvae first attack the abdominal aorta, but later on the majority of the worms can be found in the thoracic portion of the vessel. The worms advance within the aortic wall from the abdominal to the thoracic aorta. Probably, also, some of the larvae attack and penetrate the thoracic aorta directly.

The changes produced by the worms in the earliest stage are hemorrhage and purulent inflammation. This inflammation seems not to be due to secondary micro-organisms, but to by-products of the worms. It is not as intensive a process in the thoracic as in the abdominal aorta.

The larvae penetrate through the tissue of the aortic wall in the thoracic region. While the majority of the worms probably migrate out of the aorta to the adjacent portion of the intestinal tract, some of them die in the aortic wall.

The lesions that have been found in naturally infected dogs are a succession of changes of purulent inflammation of the aortic wall, with a destruction of muscle and elastic elements and a replacement of these elements with growths of dense fibrotic and fibroblastic tissue.

The advanced aortic lesions in naturally infected dogs are directly comparable with the verminous lesions of the aorta in cattle and water-buffaloes and with those of the ileoceocolic artery in horses. The earlier lesions are described here for the first time.

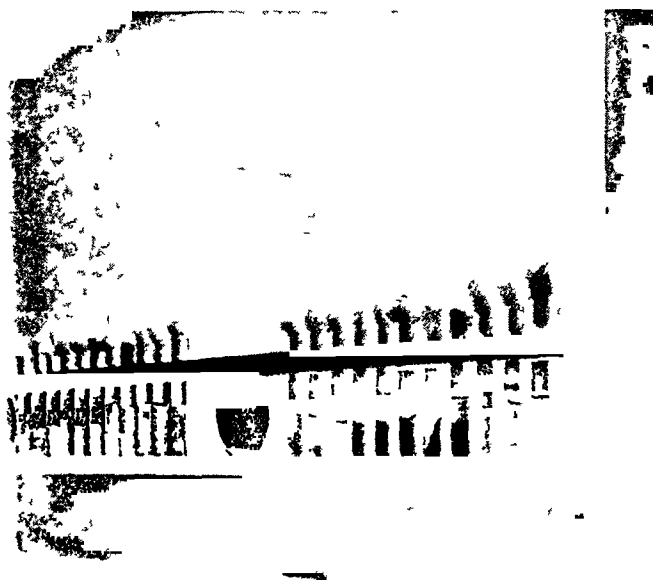
# Laboratory Methods and Technical Notes

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## WINDOW DEMONSTRATION IN TEACHING BACTERIOLOGY

DAVID L. BELDING, M D, BOSTON

The teaching of medical bacteriology requires not only didactic methods for the purpose of correlating laboratory work with clinical medicine, but also an efficient, time-saving arrangement of demonstrations and laboratory work by the students. Since the student's time in the laboratory is limited and the bacteriologic characteristics of organisms have little clinical application, in many medical schools instruction in the practical routine of hospital and public health examinations has replaced, in large measure, the study of organisms as outlined in the descriptive chart. The window demonstration offers a partial solution of the problem of retaining certain favorable features of the older methods of teaching bacteriology while entailing a minimal expenditure of time on the part of the student.



Wooden frames, similar to gigantic test tube racks, consisting chiefly of two horizontal strips, as shown in the accompanying figure, are built across classroom windows, which are readily accessible to the students. The racks hold culture tubes and plates containing the various mediums designated in the descriptive chart, and, in addition, have space for special demonstrations.

The laboratory work on a particular organism or group of organisms in the class room is confined chiefly to diagnostic procedures or problems. In addition, the students are furnished with pure cultures for microscopic examination. From the window demonstrations, the macroscopic growth and biologic characteristics of the bacteria on the various mediums may be recorded by the students on a modified descriptive chart without any appreciable loss of time, at any convenient opportunity during the laboratory period.

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\* From the Boston University School of Medicine

# General Review

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## TRAUMA AND TUMORS <sup>1</sup>

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The consideration of a single trauma as either the direct exciting cause or one of the contributory causes of a neoplasm recurs in medical literature from time to time because it possesses several interesting aspects, no one of which has ever been thoroughly understood. At an early period, beginning with 1870, many pathologists were led to serious scrutiny of the subject because of a widespread interest in the etiology of tumors, especially after the publication in 1868 of Virchow's<sup>1</sup> theory of chronic irritation. With the publication in 1877 of Cohnheim's theory of embryonic remnants, and with the development of new methods of microscopic technic and of bacteriologic and immunologic investigation, beginning with Pasteur in 1880, inquiry was begun into all the factors of possible importance in tumor causation. Then began an attempted evaluation of the importance of both single and repeated mechanical traumas. This early period of investigation covers the years between 1870 and 1880, during which several papers appeared, none, however, of any particular ultimate value.

Fresh interest in the subject arose after 1900, and especially during the subsequent decade, although scarcely a year has passed since without some serious renewal of the discussion. This recent period coincides not so much with the theoretical interest in the etiology of tumors as with the increasing legal responsibilities of employers to employees and the increasing claims made by the latter for compensation for disability resulting from injuries. During the last fifteen years this practical aspect of the subject has again led to a demand for the solution of the problem of the traumatic factor in tumor. Many judicial opinions which are available in such texts as Engel's<sup>2</sup> and Lowenstein's<sup>3</sup> have not always been brought to the attention of the American medical and legal authorities.

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<sup>1</sup> Submitted for publication, June 1, 1928.

<sup>2</sup> From St. Luke's Hospital.

1 Virchow, R. *Die Krankhaften Geschwulste*, Berlin, 1863, p. 35. Lubarsch. *Die Virchowsche Geschwulstlehre und ihre Weiterentwicklung*, Virchows Arch. f. path. Anat. **235**:235, 1921.

2 Engel, H. *Die Beurteilung von Unfallfolgen*, Berlin, 1913, p. 340.

3 Lowenstein, S. *Ueber Unfall und Krebskrankheit*, Tübingen, 1910 (bibliography), also *Beitr. z. klin. Chir.* **69**:533, 1910, **69**:693, 1910, **74**:715, 1911, and **76**:750, 1911.

The present paper is concerned, therefore, with presenting a résumé of the literature on the relationship between trauma and the production of a tumor, especially of those papers which have extended beyond a mere compilation of the statements of patients' opinions <sup>4</sup>

The various decisions made in this country under the workingmen's compensation laws have been frequently rendered without regard to the scientific aspects of the questions at issue, and both legal and medical opinions are often expressed without a clear conception of the nature of the evidence or an accurate knowledge of the facts on which the opinions are based

Present day thought finds it almost impossible to regard any one agent as the sole cause of a disease, even a disease of so limited a type as cancer. This point Gaylord, von Hanseemann <sup>5</sup> and Ewing <sup>6</sup> in their reviews of the subject frequently stressed. Even in the infectious diseases, heredity, constitutional predisposition and other contributory causes are so generally implicated that a single indispensable exciting agent is readily questioned. Tuberculosis, for example, is believed to be so intimately associated with environmental, nutritional and hygienic factors that the bacillus of Koch does not perhaps always receive its just share of blame. And so, in the case of tumors, one inclines to involve several factors—chronic irritation, possibly an inherited predisposition, degenerative lesions, physiologic changes and the wear and tear of bodily activity. It is this tendency to seek for multiple causes which has led some writers to consider a single trauma and its resulting reparative and exudative processes to be a special and directly exciting cause of tumor. This notion is still firmly fixed in the lay mind, but with the great increase in precise knowledge of the proximate cause of cancer, as experimentally demonstrated in the past decade, the attitude of the student of cancer has changed. The tar cancer of mice and rabbits discovered by the Japanese, the gastric cancer of rats shown by Fibiger to be due to a nematode, the sarcoma of the liver in rats produced on a

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4 It is obviously impossible to record here within reasonable limits the clinical histories of the thousands of cases of tumors alleged to have been produced by traumas. A few cases have been selected out of a vast number, some to illustrate the lack of logic which characterizes many of the case reports, and others to record cases which have been carefully observed and in which, if ever, the possibility of the production of the tumor is recorded. The bibliography, which has been carefully verified, offers to any one who wishes to read the detailed records, an opportunity to consult them. Much of what has been published is utterly unprofitable to read. Statistical elaboration of a thousand such incorrect histories would not furnish facts of value. The stream cannot rise higher than its source.

5 Von Hanseemann. *Ztschr. f. Krebsforsch.* **15** 492, 1916.

6 Ewing, J. *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

large scale by Bullock and Curtis, the x-ray cancer in man, have led the majority of the oncologists rather to incriminate more and more some type of chronic irritative process as the only known inciting agent of cancer and to doubt the efficacy of a single trauma in the direct production of a malignant neoplasm. It has never been possible to produce a malignant growth experimentally in animals by a single trauma.

The present discussion is restricted so far as possible to a survey of the cases of tumor believed to have been caused by a single trauma as opposed to cases caused by repeated chronic irritation of a mechanical or chemical type. The latter have been extensively studied by numerous cancer research workers, and have been found to have little relation, in any case, to the effects of a single injury. These two groups of cases can, perhaps, never be entirely separated because many of the tumors ascribed to single injuries have arisen each on the basis of a scar of many years' duration, which originally was caused, no doubt, by a single laceration, blow or contusion. On closer examination however, it is to be noted that many a scar, although incited by one such agent, has continued as a demonstrable lesion over a period of years because of the presence of foreign material which was implanted in the beginning, or possibly because of a prolonged infection. It is generally accepted that keloids and other hypertrophic scars often contain some foreign material, even if racial and individual reparative processes add complicating factors. One of the best known facts in medicine is that tissues have the capacity to heal completely and the scar to atrophy in the course of a year or two. The tissues then become so nearly normal, if foreign bodies are not present and there has not been any gross disturbance of the circulation, that a tumor arising in an atrophic scar cannot be understood to bear any relation to the preceding injury.

Nearly all the literature purporting to prove that tumors are directly caused by single traumas includes, also, as traumatic causes, the chronic inflammatory diseases, such as mastitis and chronic cervicitis, and the ulceration produced by parasites and chemicals. It is well known, however, that all of these require continuous applications of the irritants for long periods, throughout which not only one but many stimuli are added. These, therefore, are entirely excluded from the present consideration. Their etiologic importance has been repeatedly and accurately discussed in the literature dealing with tumors, because these phases of the subject are of interest to the scientific mind because experimentally demonstrable, whereas the etiologic importance of single trauma is no longer a matter of genuine interest to this group, partially because the subject was discarded years ago by many of the great leaders in pathology after careful research had been carried out. It has been revived not by the scientific group but by commercial interests, because

of the increasing accessibility of compensation for any injuries sustained while in the discharge of any kind of employment, especially if the presence of a tumor in an employee gives countenance to the idea that it may have had a traumatic origin

#### EXPERIMENTAL RESEARCH

A large amount of experimental work was done by Lubarsch,<sup>7</sup> Ribbert<sup>8</sup> and others. That of Lubarsch was perhaps the most intelligent. He utilized many series of animals, the tissues and tumors of which he traumatized in the hope of ascertaining what effect mechanical forces could exert on the rate of growth of normal or neoplastic tissues. He inoculated sarcoma into mice and rats and also traumatized spontaneous fibroadenomas of the breast in rats and epitheliomas of the dog for a minute at a time with a percussion hammer. He also crushed these growths with forceps, and injected homologous and foreign blood over a period of weeks or months, but he did not observe any increase in the rate of the growth of the tumors. The breast tumors were unchanged morphologically, and the mitotic figures were not increased. In mice that had two tumors, the traumatized one at times regressed or remained the same size, while the other grew. It was Lubarsch's conclusion that trauma could be accepted as a factor in growth only if (a) the violence was severe, was localized and caused long continued injury at the same point as that at which the tumor later appeared, and also if (b) the histologic structure of such a tumor made it appear reasonable that the growth was due to the injury. He found no regressive effect unless the blood supply was cut off. There are, however, recorded examples of human tumors which receded for long periods after partial excision.

Ribbert also investigated this subject and performed many implantation experiments in the attempt to produce epitheliomas. His experiments were motivated by the work of Cohnheim and if malignant tumors had resulted the work would probably have greatly strengthened Cohnheim's hypothesis as to the etiologic importance of misplaced embryonal rests. Such experiments with great uniformity led only to discouraging results, as an implantation dermoid cyst appeared to be the only tumor which he could produce with any regularity. Absolutely no malignant tumors resulted.

Barfurth<sup>9</sup> also attempted to produce tumors by mechanically displacing the cells of sea urchin's eggs in the gastrula stage, but instead of tumors, he formed only simple dermoid cysts. Traumatized tissues, both embryonic and adult, have been repeatedly introduced into animals

<sup>7</sup> Lubarsch. *Med Klin* 8 1651, 1912

<sup>8</sup> Ribbert. *Deutsche Ztschr f Chir* 47 574, 1898

<sup>9</sup> Barfurth, Merkel-Bonnet. *Anatomische Hefte*, 1893, sect 1, no 9

by Zahn<sup>10</sup> and many others. Fetal cartilage and bone were implanted by Zahn under the capsule of the kidney. Birch-Hirschfeld and Garten<sup>11</sup> injected embryonal tissue into the vena cava of animals. This produced growths in both the liver and the lungs for a short time, but these eventually receded and tumors were never produced. Nichols<sup>12</sup> inoculated rabbits and guinea-pigs with cells of various organs but failed to obtain malignant growths. Only Askanazy<sup>13</sup> and Carrel<sup>14</sup> succeeded in producing malignant tumors in the rat and fowl, respectively, by injection of embryonic material plus minute quantities of arsenic. Obviously, these results with embryonic tissue did not have anything to do with the question of producing tumors by traumatic injury of adult cells.

Cohnheim and Maas<sup>15</sup> and Fischer<sup>16</sup> also tried to form bony tumors by introducing periosteum and cartilage into veins, but without success. Leopold<sup>17</sup> implanted cartilage subcutaneously, also without results. Gland grafts likewise were done in great numbers and often succeeded temporarily, but tumors did not result.

It is unnecessary to cite further examples of this type. The most recent bibliography of bone grafting is in a paper by De Jong and van der Kemp<sup>18</sup>. If such grafting of foreign cells in normal tissues really produced neoplasms, every patient undergoing an osteoplastic operation would be in grave danger.

Slye<sup>19</sup> described eighty-seven sarcomas in mice, in eleven of which the tumor was believed to have arisen at the site of a previous injury. In these cases, either the locality of the injury was noted and it was observed that afterward a sarcoma made its appearance at this point or a tumor was observed at the site of a scar from some old injury. Proof was not offered that any of these sarcomas were directly produced by the traumas (bites), and experiments were not done to show the susceptibility of the strains studied to a type of injury which might produce a tumor without an intermediary process such as chronic inflammation or scar production. In the rats, an animal in which sarcoma is the most frequent type of tumor, sarcoma formation was not observed to

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10 Zahn. *Virchows Arch f path Anat* **95** 369, 1884

11 Birch-Hirschfeld and Garten. *Beitr z path Anat u z allg Path* **26** 132, 1899 (bibl.)

12 Nichols. *J M Research*, n s **8** 221, 1904

13 Askanazy. *Verhandl d deutsch path Gesellsch* **21** 182, 1926

14 Carrel, A. *Compt rend Soc de biol* **93** 1083, 1925

15 Cohnheim and Maas. *Virchows Arch f path Anat* **70** 161, 1877

16 Fischer. *Deutsche Ztschr f Chir* **17** 61 and 362, 1882

17 Leopold, G. *Virchows Arch f path Anat* **85** 283, 1881

18 DeJong and van der Kemp. *Beitr z path Anat u z allg Path* **79** 268, 1928

19 Slye, Holmes and Wells. *J Cancer Research* **2** 1, 1917



follow bites in a large series of animals under close observation Both species of rodents frequently bite their cage mates, and yet superficial tumors are rare (Curtis <sup>20</sup>)

#### CLINICAL OBSERVATIONS

Aside from such experimental work, it must be realized that the only other available material on which to base conclusions is compilations of case histories Early it was observed by Schimmelbusch <sup>21</sup> that such material as this rendered any conclusion impossible because scientific matters could not be decided on the basis of unreliable and untrustworthy evidence and that, on this subject, all the evidence is essentially unreliable Askanazy <sup>22</sup> stated that the literature dealing with the subject was only a "collection of anecdotes" and that there were many highly uncritical studies in the literature This seemed so important a verdict to many that in 1909 a set of postulates were expressed by Thiem <sup>23</sup> in the hope of directing attention to the need for soundness in analysis of case records and to the unreliable character of much material hitherto accepted as valid

The clinical evidence may therefore be divided into two classes one embracing the large tabulation of histories drawn from hundreds of hospital records, all used as evidence without regard to the honesty, the mental capacity or the motives of the patients, the other, the small number of papers published by judicial pathologists, each recording perhaps a single case which to the writer appeared to suggest that a definite relationship might exist between the tumor and the trauma Even in these cases there remains only the post hoc propter hoc type of logic, and no matter how much one may respect the powers of accurate observation shown by these pathologists and the integrity of their statements, one is bound to note that most of their papers, also, arbitrarily assume the importance of the trauma as an observed external factor Ribbert, <sup>24</sup> who thought that all the statistical collections were without value, stated that well studied single cases of this type might be more convincing than any heretofore published statistics

The early literature is more confusing than helpful and contributes practically nothing to the subject The dissertation of Siegfried Wolff, <sup>25</sup> which appeared in 1874, is often quoted because the author made an

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<sup>20</sup> Curtis, M R Oral communication

<sup>21</sup> Schimmelbusch, quoted from Machol by Lubarsch-Ostertag *Ergebn d allg Path u path Anat* **1** 527, 1895

<sup>22</sup> Askanazy, quoted from Sauerbruch *Deutsche Ztschr f Chir* **199** 1, 1926

<sup>23</sup> Thiem *Handbuch der Unfallkrankungen* ed 2, Stuttgart, 1909, p 589

<sup>24</sup> Ribbert *Zentralbl f Chir* **25** 1195, 1895

<sup>25</sup> Wolff, Siegfried *Zur Entstehung von Geschwulsten nach traumatischen Ernwirkungen*, Inaug Diss Berlin 1874

attempt to survey all the cases of tumor that had appeared in the University Surgical Clinic in the preceding ten years and to determine the frequency of trauma in these cases. The paper includes many cases which indicate a relationship between the tumors and chronic mechanical irritation due to foreign bodies, scars due to burns and lacerated wounds, but does not present any clinical evidence that is pertinent to the importance of the single acute trauma. Only one case, that of a carcinoma of the breast, is even worthy of mention, it will be cited in the following pages. Wolff enumerates, therefore, so few cases of single trauma followed by carcinoma, and these of such dubious certainty, that his conclusions should not be quoted in this connection.

On the subject of sarcoma caused by a single trauma, Wolff has been quoted as offering slightly more evidence, but in many of the cases that he cites, the injury was not at the exact point of the subsequent tumor and in many the tumor appeared only following a fracture or a contusion, of 100 cases of sarcoma of all types, 20 were found to have been preceded by traumas. A critical study of these cases was not made by Wolff.

The lengthy paper of Lowenthal,<sup>26</sup> appearing in 1895, contained a survey of 358 cases of tumors each preceded by an acute trauma, from among 800 observed at the Pathological Institute at Munich from 1870 to 1895. This paper has been widely quoted because of the large number of cases reviewed. So little critical survey of these cases has been made and the hospital histories have been employed so freely as evidence that little is contributed for the acute and no more is proved for the chronic types of traumatization.

Lowenstein,<sup>3</sup> in 1910, in a long monograph on the subject, analyzed 261 cases of malignant tumor compiled from the literature, 7 from the Samariterhaus at Heidelberg and 3 from Frankfurt, all probably traumatic, according to the histories. This paper is superior to others because an attempt was made to apply critical standards to the histories, and the author appreciated the need of sound methods of judging case records. Tables are presented giving clearly the lapse of time between the injury and the development of the tumor, and he included only cases in which the injury was described as at the exact site of the subsequent tumor. This marked a new type of study of the records on the subject and indicated the increased critical attitude then beginning to show itself.

This paper followed the publication by Thiem of an important contribution revealing a change toward precision of thought, for in 1909 Thiem<sup>23</sup> formulated a set of postulates which have since been of great value in clarifying the subject. Thiem pointed out that, in coming to a decision as to the importance of trauma, it must be remembered that

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<sup>26</sup> Lowenthal, C. *Arch f klin Chir* 49 1, 1895 (bibl.)

trauma does influence the localization and course of other diseases, such as tuberculosis, osteomyelitis and pneumonia, although specific causative factors are well known for these diseases. Therefore, even "if several cancer parasites" should be discovered, the factor of trauma might still be important. Nevertheless, he wrote that "trauma is not the real cause of tumors" and that "among the accessory causes it plays a very important rôle."

Thiem's postulates were (1) that definite proof of the accident must be offered, (2) that the trauma must have been of sufficient severity to be effective, (3) that the tumor need not be at the exact site of the injury but must be definitely related to it, as is *contre-coup* laceration of the brain, and (4) that the interval between the accident and the appearance of the tumor must be a reasonable one, for sarcoma, this was stated by Thiem to be not under eight days, and for carcinoma, not under three or four weeks. At present, students of tumors would not accept these shorter intervals, because of the large amount of accurate knowledge which has been recently accumulated to show that a much longer time is required. In 1913, Graef<sup>27</sup> published a more complete monograph, contributing a collective review with a bibliography of 161 references. The author restricted his cases to those with only a single acute trauma. This paper includes also summaries of the more important monographs, and the general statistics are based on the cases as included in these various papers. Many of the cases he included, however, though following acute trauma, were preceded by old scars, irritation with foreign bodies and other irritants of various types, and therefore should not properly have been included. While the paper is useful and is written with considerable understanding, Graef without much discrimination allowed unimportant contributions to appear in it. This applies especially to many of the cases of carcinoma cited, those, for example, of the internal organs. Graef was, on the whole, skeptical as to the real relationship between trauma and tumor and advised great caution in assuming a direct relationship.

American literature contains three brief papers of real value, giving excellent reviews of the general situation. One is that by Ophuls,<sup>28</sup> published in 1921. Although brief, it is conservative and clearly formulates the absolutely essential conditions which must be complied with in awarding any verdict.

The second, by Mock and Ellis,<sup>29</sup> published in 1926, covers much the same ground and describes nine cases believed by them to fulfil

<sup>27</sup> Graef, W. *Centralblatt für Grenzgebiete der Medizin und Chirurgie* **17** 603, 1913 (bibl.)

<sup>28</sup> Ophuls, W. *California State Journal of Medicine* **19** 54, 1921

<sup>29</sup> Mock and Ellis. *Trauma and Malignancy*. *J. A. M. A.* **86** 257 (Jan. 23) 1926

many of the postulates that would place the cases in the group of neoplasms related to traumas and therefore entitle the patients to compensation, even though the tumors were not necessarily caused by the injuries. The authors pointed out the obligation of the surgeon to decide whether or not a particular case of malignant growth could be ascribed definitely to trauma, and they stated that there is no justification for deciding this in any particular case unless a relationship can be proved with scientific accuracy, and that cases as commonly reported offer no such scientific proof.

The third paper, also published in 1926, by Ewing,<sup>30</sup> calls attention to the requirements which he regarded as necessary to a sound verdict, and cites one carefully observed instance of a tumor arising after an injury and believed by him to be due to it. The paper is valuable, also, because of the concrete expression of opinion with regard to the rôle of trauma in definite types of tumors. His is a simple statement which, if followed, would rule out many of the cases now under discussion in the courts. The requirements laid down by Ewing are clear and closely in accord with those of Thiem, but are perhaps more definite, and in discussion of them the author especially warned against certain fallacies. These requirements are as follows:

- 1 The authenticity and the sufficient severity of the trauma must first be established.

- 2 The previous integrity of the wounded part must be shown. Lowenthal did not require this, and for that reason Ewing justly eliminated his paper from consideration as a valuable scientific contribution.

- 3 The identity of the injured area with the site of the subsequent neoplastic growth must be demonstrated.

- 4 The tumor must be shown to be a type which could result from trauma. Under this heading the author eliminated tumors due to congenital rests.

- 5 The proper interval of time must be proved to have elapsed.

For practical purposes these requirements, which have gradually been evolved from the experience of physicians and pathologists during the last fifteen years, are of the greatest importance. While they do not reach, and cannot reach, the theoretical truth, it is obvious that they are all that can be adhered to by any one forced to make a decision in a concrete case.

*Authenticity of the Trauma*—The question of the authenticity and severity of the trauma is largely a legal one and is of no interest from

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<sup>30</sup> Ewing, J. Am J Surg 40 30, 1926

the medical point of view. It is well known that it is frequently impossible to establish authenticity by the accounts of eye witnesses, who are often far from observing the truth, and that the severity of a trauma has therefore to be judged by its objective results rather than by its aspect to the patient at the moment of its infliction or in retrospect. It is well known that the possibility of financial gain adds greatly to the importance of many traumas, in the minds of the patients, and that injuries are constantly suffered which are forgotten when the opportunity to gain from them does not present itself.

*Previous Integrity of the Wounded Part*—It is also becoming evident that to demonstrate that the tumor process had not already begun before the time of the injury is often impossible. Before the frequent roentgenographic study of injured tissues, especially in the neighborhood of the bones, this was much more difficult than it is at present. Most of the reports in the literature, it must be remembered, described persons who when they presented themselves had swollen traumatic lesions. But the injured areas were not immediately subjected to x-ray studies in the clinics. Now such lesions are immediately examined with the x-ray, and the cause of the hemorrhage or exudate often then becomes apparent. Even in a phalanx a pre-existing lesion of the bone may be found indicating a long-standing disease process. In one instance in which a typist broke her finger while writing, a hitherto unrecognized cystic chondroma was promptly demonstrated in a roentgenogram. In the bones of the forearm or the leg, chondromas or giant cell tumors not infrequently have in this way been discovered, and in the thigh and upper arm a destructive sarcoma, such as occurs more frequently in this region, may be found to have caused the absorption of bone. Such a tumor is entirely unknown to the patient, who in perfect good faith may state that a jar or fall, as in a trolley car, was the cause of a fracture of the bone. Surgical intervention in this case discloses a small amount of highly vascular tumor which has originated in the shaft of the bone, although the greater proportion of the mass consists only of blood and could be easily mistaken for a hematoma even on microscopic examination. All injuries that are likely to be cited in claims for compensation should therefore be required to be subjected to study by the x-ray when the patient is first seen, if a trauma in or about the bone can possibly be implicated. The lengthy series of cases hitherto reported in the literature would be more useful and more interesting if such studies had been made.

*Identity of the Injured Area with the Site of the Neoplasm*—It would seem evident that the trauma must bear some direct anatomic relation to the situation of the tumor. According to Ewing, the sites

must be identical. He assumed also that the well known results of transmitted injury, such as a tear in the meninges or the cortex from a blow on the jaw, are understood to be an essential part of the primary damage. Ewing, however, denied the possibility of causing a tumor of the internal organs by external injury, thereby ruling out all intra-abdominal growths and admitting as possible one neoplasm, only, of the chest, which was reported to be due to an injury of the skeletal tissues. In this instance, also, it might be assumed quite properly that pleural adhesions, with damage to the visceral pleura, followed the external trauma and that the case belongs therefore in the group due to chronic irritation.

There are included in the literature reports of trauma to one portion of the thigh or buttock, followed after a shorter or a longer period by sarcoma of the femur of pelvis. In such a case, a direct anatomic relationship cannot be established between the point at which the trauma was inflicted and that at which the tumor appeared. But, according to the laws of mechanics, the maximal injury is sometimes transmitted to a different point from that at which the injury is applied, as, for instance, in the case of a Colles fracture of the wrist. These principles have not always been taken into consideration in the published records. I have not found examples of bone or periosteal sarcoma reported as found in the hundreds of thousands of cases of calluses which must have resulted from the Colles fractures which are seen every year.

In this connection may be mentioned one of the only two cases which L. Pick<sup>31</sup> considered worthy of consideration. It was a fibrosarcoma of the humerus, which appeared as a swelling over the bone in May, 1927. The patient had sustained a compound fracture of the ulna in June, 1918, with resulting infection and sequestrums. The arm was healed in September, 1923, and the tumor did not appear until May, 1927. Here again there is confusion of thought as between a chronic and an acute trauma. The acute trauma preceded the appearance of the tumor in this case by nine years, and irritation was no doubt present over most of this period. Lubarsch,<sup>32</sup> however, expressed the belief that a hard fibrosarcoma might possibly follow an injury by three or four years.

*Required Lapse of Time*—The interval of time which must elapse between the injury and the appearance of the tumor in order even to suggest a causal relationship, as reported in the literature, is extremely variable. Most of the figures in the literature, however, are drawn from patients' statements as to the correlation.

31 Pick, L. *Med Klin* **17** 416, 1921

32 Lubarsch, quoted by Pick. *Med Klin* **17** 416, 1921

Ziegler<sup>33</sup> stated that the tumor must be visible as soon as the acute swelling of the trauma has subsided, and Ribbert believed that the time must be at least short, but did not arbitrarily specify any period. Bérard<sup>34</sup> and Thiem<sup>23</sup> more or less agreed that the time for the development of a sarcoma might be from eight days to one year, for carcinoma, from three weeks to three years and for glioma, from one month to ten years. Villata<sup>35</sup> stated that it must be from a few weeks to eleven years. Ewing<sup>30</sup> called attention to the fact that some tumors are of slower growth than others and pointed out that an advanced sclerosing osteogenic sarcoma of one of the long bones certainly requires "months" to be large enough for detection, and that inside this period such a tumor cannot possibly have been caused by the trauma. Virchow,<sup>1</sup> on the other hand, recognized the fact that bony metastases could develop rapidly, but did not specify any time, and Edward Miller<sup>36</sup> showed from x-ray plates and autopsy records that large nodules of round cell sarcoma developed in the lung in two and one-half weeks. Round cell sarcoma and lymphosarcoma are, however, known to be tumors of extremely rapid growth, as can often be observed in subcutaneous nodules. The writers who believed that glioma is related to trauma accepted a much longer interval of time between the trauma and the appearance of symptoms, Bérard stated that it might be ten years, and other writers considered that it might be even from thirty-five to forty years.

It is because of the uncertain duration of this interval that an attempt has been made to establish the importance of bridging symptoms which might seem to connect in some way the injury with the trauma, Ziegler having stated that unless the tumor appears immediately, there must be intermediate related symptoms. These are generally either intermittent or continuous pain, and are therefore very difficult to evaluate because there are seldom objective symptoms to add weight to the patient's statements.

Sometimes the interval between the trauma and the tumor has been assumed to be extremely short, even a few days, and therefore it might be well to recall that in a short-lived animal like the mouse, tail cancer rarely appears until three months have elapsed, and that in the rat sarcoma due to the injury inflicted by *Cysticercus* apparently requires at least eight months from the beginning of the irritation to the demonstration of

33 Ziegler, E. *Munchen med Wchnschr* **42** 621 and 650, 1895

34 Bérard, L. *Conference internationale pour l'étude du cancer*, Paris, 1910  
p 355

35 Villata, G. *Policlinico* **32** 451, 1925, abstr, *J A M A* **85** 1338 (Oct 24) 1925

36 Miller Edward. *IX Congress der deutschen Roentgengesellschaft*, 1913

a tumor, and yet both these agencies are extremely effective carcinogenetically, giving rise to a high percentage of tumors in suitable strains. Such periods in these short-lived rodents are comparable with periods of from five to ten years in man. The same long period has been found to elapse in a case of chronic dermatitis due to irritation by the x-ray before the appearance of a neoplasm, yet this type of chronic irritation is also effective in the production of cancer. In the light of these facts it seems difficult to believe that a single injury inflicted a few weeks before, can act as an effective cause of a neoplasm.

#### BENIGN TUMORS

It is generally conceded that few benign tumors bear any relationship to acute trauma. In all the statistics devoted to this subject, they are regarded as less numerous than the malignant ones. It is of interest that Lowenthal and other writers, however, who found a high percentage of malignant tumors related to single traumas also found a higher percentage for the benign ones. For instance, Lowenthal, who believed that 84 per cent of the malignant tumors were caused by traumas, also claimed that 16 per cent of the benign tumors had this etiology. On the other hand, Wurz,<sup>37</sup> among 129 benign tumors, found only 3 per cent in which there appeared to be the slightest relationship to single traumas. Beraud<sup>34</sup> pointed out that many benign growths were classed as tumors in the literature, which actually were only inflammatory lesions, which are known to be sometimes related to traumas. But he included here, as inflammatory, the lipomas, the fibrolipomas and the myxolipomas and the osteomas of the cranium, forearms and adductors, a classification which would by no means be adhered to by most writers. It is also a matter of terminology whether an organized hematoma is sometimes classed as an angioma, or whether its inflammatory nature is recognized at the time it is examined. The epithelial cysts, which are generally admitted to be traumatic, were shown by Hesse<sup>38</sup> to be due frequently to epithelization of hair follicles and other derivatives of epithelium.

*Lipoma*—Wurz<sup>37</sup> carefully analyzed the histories of twenty-eight patients with lipoma and concluded that only one of the tumors could be suspected of being a traumatic one. The patient, a woman, had sustained a fall in which the left side of the pelvis was seriously contused and she had suffered continuous pain in the buttock for a few weeks, then, on examination, a large lipoma, apparently actively growing, was found embedded in the fat. This tumor might be placed in

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37 Wurz, K. Beitr. z. klin. Chir. **26** 567, 1900

38 Hesse, F. A. Beitr. z. klin. Chir. **80** 494, 1912



the group of fat necroses described by Lee and Adair<sup>39</sup> and may have been only an instance of active regeneration and not of neoplastic growth, or a preexisting tumor may have been rendered painful by the contusion

Siegfried Wolff<sup>25</sup> believed four of his cases of lipoma to be traumatic. One of them followed a single injury. The others appeared on the shoulders following repeated contusions. Since this is so common a situation for lipoma, even in those whose occupations do not cause them to sustain injuries to the shoulders, its relationship to this trauma seems to be largely imaginary.

Stern<sup>40</sup> studied this type of tumor and decided that it could not be in any way connected with an injury. Bosse and Lieschke<sup>41</sup> believed that they had watched the origin of several cases of scrotal lipoma secondary to contusion, and Lieschke<sup>42</sup> collected sixty-two cases in which he believed that there was possibly a traumatic origin. These tumors, also, were described before the frequency and nature of traumatic fat necrosis and regeneration were well understood.

*Myxoma and Angioma*—Evidence has not been reported that a case of myxoma or of true angioma has ever been caused by a trauma.

*Myoma*—Myoma of the uterus is also not caused by trauma, direct or indirect. The question has been raised because of the astounding case described by Schneider<sup>43</sup> of a woman who, struck by a calf in the right lower abdominal quadrant, suffered a hemorrhage and a miscarriage. Abortion occurred in two succeeding pregnancies, and after four and a half years she was found to have a fibroid uterus. Leopold believed that the wide occurrence of fibroids among all types of women rendered it impossible to associate them with special traumas.

*Fibroma*—Cases of fibroma were studied also by Wurz,<sup>37</sup> who believed that none was referable to trauma. Graef<sup>27</sup> thought some of them might be, and Audain<sup>44</sup> referred to the traumatic fibromas and sarcomas in the Haytian negroes as malignant tumors, but these are now known to be keloids.

Sontag and Tendeloo,<sup>45</sup> quoted by Sauerbruch,<sup>46</sup> believed that the fibromas were usually traumatic, but the prevailing view at the present

39 Lee and Adair. *Ann Surg* **72** 188, 1920

40 Stern. *Ueber traumatische Entstehung innern Krankheiten*, Jena, 1913, p. 487

41 Bosse and Lieschke. *Therap Rundschau* **3** 433, 1909

42 Lieschke. *Lipom und Trauma*, diss., Berlin, 1911, quoted by Graef (footnote 27)

43 Schneider. *Unfall und Gynecologischen Erkrankungen insbesondere Myome*, diss., Munich, 1912

44 Audain, quoted by Graef (footnote 27)

45 Sontag and Tendeloo, quoted by Sauerbruch (footnote 46)

46 Sauerbruch, F. *Deutsche Ztschr f Chir* **199**-1, 1926

is that of von Hansemann,<sup>5</sup> who considered all these tumors in which there is a traumatic history, as inflammatory and due possibly to foreign bodies or infections. Many of the tumors of the anterior abdominal wall classed as desmoids are generally considered to be due to stretching lacerations or repeated contusions of the rectal muscles.

*Chondroma*—The chondromas were believed by Lubarsch not to be caused by traumas, but to be stimulated to more rapid growth by them in some cases, especially if the injury was inflicted near to the epiphyseal line of one of the long bones. Graef<sup>27</sup> thought that a few of these tumors followed fractures of the ribs and were derived from cartilage, which is usually found in a normal callus, but that the chondromas of the organs were teratoid only. Roger Williams<sup>47</sup> admitted the possibility of an osteochondroma arising in this way from the cartilage cells in the callus following fracture.

*Adenoma*—The adenomas cannot well be believed to have any relation to traumas. The inflammatory hypertrophies resembling adenomas are known to be frequent.

*Osteoma*—The exostoses and osteomas are a somewhat intermediate group, the former being classed by Wood<sup>48</sup> among the inflammatory lesions. Many of the so-called traumatic osteomas are frankly chronic inflammations in origin (rider's bone) while others are now understood to be benign bony tumors which have existed for a long time and have finally been separated from the shaft of the bone by traumas. A blow or fall not infrequently separates an exostosis from the lower third of the humerus or femur and in this way brings the tumor to the notice of the patient. Such a tumor is found to have a concave inner surface and to have been detached by the violence along this line of cleavage. Witz,<sup>37</sup> however, thought that 40 per cent of these lesions were probably traumatic and believed that it was almost the only tumor that could be so considered. Graef<sup>27</sup> admitted that a certain proportion were traumatic, but pointed out the inflammatory nature of many of the tumors so classified.

*Osteitis Fibrosa*—As osteitis fibrosa occasionally precedes giant cell tumor of the bone and is generally believed to be due to local, small, repeated hemorrhages, some writers—for example Sauerbruch<sup>46</sup>—believed that trauma may be one of the factors causing such hemorrhages and therefore ultimately a giant cell tumor, but that it is not the only cause. However, experimentally produced hemorrhages have

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47 Williams, Roger. The Natural History of Cancer, New York, William Wood & Company, 1908.

48 Wood, F. C., quoted from Delafield and Prudden. Text Book of Pathology, New York, William Wood & Company, 1927, p. 1097.

failed to cause tumors. Looser<sup>49</sup> showed a case in which nearly every bone in the body contained the lesions of osteitis fibrosa, and pointed out that in none of these was there any history of trauma.

*Giant Cell Tumor*—Ewing<sup>30</sup> believed that osteitis fibrosa may precede the hemorrhages which eventually produce giant cell tumor, but thought that there is not in such cases any traumatic history of importance. In several cases of supposed traumatic origin x-rays revealed disease of long standing. Sauerbruch<sup>46</sup> cited one case in which the patient sustained a blow on the forearm and in three months presented at the site a large giant cell tumor. Such records, are, however, infrequent. Some writers regarded the causative agent of the giant cell tumor as an infectious one.

#### MALIGNANT TUMORS

*Carcinoma—Superficial Types*—Among the malignant tumors, the squamous type of carcinoma has been only rarely ascribed to a single trauma. In each case the diagnosis invariably depended only on the statement of the patient that the part was previously normal. For instance, the case reported by Hahn,<sup>50</sup> and quoted by Machol,<sup>51</sup> was that of a patient with a lacerated wound in the scalp for which he was treated in the hospital seven weeks, he returned seven months later because of an epithelioma in the same region. Another instance described is that of a patient who was observed to have an epithelioma of the tongue following an accidental bite. However, it has been pointed out by others that epileptic patients who bite their tongues continuously have never been found to have an increased frequency of epithelioma of that organ.

When carefully analyzed, nearly all the cases indicate that the original trauma resulted in a scar which was present for some time before the tumor appeared, or else that an effort was not made to ascertain that the tissues were normal before the time of the injury. This applies to the case of Dietrich,<sup>52</sup> in which an old scar was traumatized and some three months later an epithelioma appeared. The word of the patient was accepted that a neoplasm was not present at the time of the injury. Dietrich also concluded that the traumatism caused by a biopsy resulted in a great local increase in the rate of growth of the part of the tumor incised, but the pictures submitted in evidence scarcely bear out his conclusions.

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49 Looser. *Deutsche Ztschr. f. Chir.* **189** 113, 1924.

50 Hahn, Otto. *Beitr. z. klin. Chir.* **26** 591, 1900.

51 Machol. *Die Entstehung von Geschwülsten im Anschluss an Verletzungen*, Strassburg, 1900.

52 Dietrich. *Neue Deutsche Chirurgie*, Stuttgart **35** 184, 1926.

Ewing<sup>30</sup> was uncertain as to whether it is ever justifiable to ascribe an epithelioma to an injury, and in any case he would not accept any causal relationship after one year. There are cases described as following a blow, a bite, a gunshot wound or a laceration even seventy-six years before, as mentioned by Melchior,<sup>53</sup> but in any case the two events can scarcely be shown to be related.

*Carcinoma of the Breast*—Carcinoma of the breast is one of the types of carcinoma most frequently ascribed to injury, largely because the gland is superficial and subject to injuries, and because the tumors are difficult to palpate and generally painless until some special trauma causes structural changes due to hemorrhage. To ascribe the origin of a carcinoma to a single blow is as inaccurate and unscientific as it would be to judge of the duration of a tumor of the breast from the patient's statement, and any one who listens carefully to the statements of patients knows that carcinomas of the breast are generally stated to have been present for from five years to two days without regard in any instance to the size, position or type of the tumor. Compilations in the literature by Dietrich,<sup>54</sup> Frangenheim,<sup>55</sup> Schulthess,<sup>56</sup> Winwarter,<sup>57</sup> Oldekop<sup>58</sup> and Ziegler<sup>33</sup> contain statements indicating that trauma preceded the tumor in from 1 to 25 per cent of the cases. This wide range of figures indicates only the impossibility of drawing accurate conclusions from the statements at hand.

Wurz<sup>37</sup> stated that of 163 cases probably none was traumatic, and that in only 5 per cent can it even be suggested that a trauma was responsible for the tumor.

Graef<sup>27</sup> thought that Lowenthal's<sup>26</sup> twelve cases in the male breast should be discarded, as the rapidity of the growth of carcinomas of the breast in the male is well known. The three descriptions of cases by Machol<sup>51</sup> are entirely uncritical, as is most of his paper, some of the tumors that he cited developed a year after minor injuries, and one of them was never diagnosed microscopically.

Ewing<sup>30</sup> stated that a carcinoma of the breast can be assumed to have followed an injury only if the breast can be shown to have been previously normal and the injury to have been severe enough to have caused interstitial hemorrhage and solution of continuity of the breast ducts, also that there must be some indication of continuity of symp-

53 Melchior. *Munchen med Wchnschr* **63** 371, 1916.

54 Dietrich. *Die Erkrankungen der Brustdruse*, Neue Deutsche Chirurgie, Stuttgart **35** 184, 1926.

55 Frangenheim, P. *Zweifel-Payr, Klinik der bösartigen Geschwulste*, Leipzig, 1925, vol 2, p 663.

56 Schulthess, H. *Beitr z klin Chir* **4** 445, 1889.

57 Winwarter. *Beitrag zur Statistik der Carcinom*, Stuttgart, 1878.

58 Oldekop, J. *Arch f klin Chir* **34** 536, 1879.

toms between the trauma and the appearance of the tumor and that even in these cases one can only maintain a probable relationship. He believed that the masses due to fat necrosis and regeneration resemble cancer, but stated that such a lesion is never followed by cancer.

*Tumors of the Internal Organs*—It is almost universally agreed that tumors of the internal organs are not caused by single external injuries, but by chronic inflammatory processes and long continued traumatization. Ewing<sup>59</sup> stated that in the internal organs cancers can result only from long continued irritation, that gastric, rectal, pancreatic, hepatic and uterine tumors are so caused, and that neither these nor tumors of the lung, esophagus and gallbladder can be ascribed to acute traumas. Boas,<sup>59</sup> who collected a series of sixty-two cases of gastro-intestinal carcinoma which were alleged to be related to trauma, found that usually the asserted relationship was not possible, for example, a carcinoma of the pancreas had been alleged to be due to a fall on the back, and a carcinoma of the pylorus, to a fall on the sacrum. As such claims were manifestly absurd, he admitted only nine cases in which he thought even the slightest relationship might be indicated. Gockel,<sup>60</sup> in a lengthy article, described the chronic irritants which he believed were the only important agents in the production of tumor in these situations. Graef<sup>27</sup> believed that there was little, if any, relationship and that carcinoma of the stomach could never be caused by a trauma unless the trauma were severe enough to cause an ulcer in which the tumor finally developed. Menne<sup>61</sup> collected from the literature cases of this type in which compensation was awarded and cases in which it was refused.

*Lymphosarcoma*—Pistocchi<sup>62</sup> recently described a lymphosarcoma of the stomach appearing five months after a severe contusion of the epigastrium with intense pain in the interim. The same degree of trauma, however, is frequently sustained by laborers and especially by prizefighters, without any known injury to the stomach. Lymphosarcoma of the stomach, in fact, is one of the rarest of the tumors. Furthermore, no one asserts that the commonly occurring lymphosarcoma of the cervical nodes is of traumatic origin.

*Hypernephroma*—Hypernephroma of the kidney and the suprarenal gland is believed by most pathologists to be due always to a congenital rest, its occurrence does not bear any relationship to trauma. Ruckart,<sup>63</sup> in a compilation of 117 cases in the literature, found trauma

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59 Boas. *Deutsche med. Wchnschr.* **23** 707, 1897.

60 Gockel. *Arch. f. Verdauungskr.* **2** 461, 1896.

61 Menne, Ed. *Deutsche Ztschr. f. Chir.* **81** 374, 1906.

62 Pistocchi, G. *Policlinico* **30** 83, 1923.

63 Rückart. *Deutsche med. Wchnschr.* **49** 384, 1923.

mentioned only nine times, and himself thought that in each case the trauma had called attention to the tumor rather than caused it. Ribbert,<sup>64</sup> also, believed that the Grawitz type of tumor arises only from congenitally misplaced cells.

Sauerbruch,<sup>65</sup> on the other hand, observed a patient who had sustained a blow in the lumbar region severe enough to keep him in bed for three weeks, and who later appeared with an inoperable tumor in the region of the kidneys. The fact that he observed hemorrhage in the region of the tumor at autopsy cannot be adduced as evidence, since nearly all suprarenal tumors of any large size are hemorrhagic, even those in patients who have been in bed for months. Frangenheim,<sup>66</sup> however, considered the possibility of stimulating a quiescent suprarenal tumor of the cortex to active growth by traumatization.

*Pulmonary Tumor*—A serious effort has never been made to ascribe pulmonary tumor to an injury. The case reported by Lepine<sup>65</sup> was that of a man who had sustained an injury to the chest wall and who one year later developed a squamous carcinoma of the lung beneath the site of the old injury. But serious injuries to the chest are so frequent and pulmonary tumors so rare that, statistically, a causal relationship is not even suggested.

*Choroidal Sarcoma*—Sarcoma of the choroid has sometimes been claimed to be due to trauma, chiefly on the ground of its being vascular and hemorrhagic. Sattler<sup>66</sup> pointed out that it is not traumatic and he did not admit even that it can follow the chronic inflammations of the eyeball.

Wintersteiner<sup>67</sup> studied ninety cases of sarcoma each reported to have been caused by trauma but could find only four in which there seemed to be any possibility of it.

*Testicular Tumor*—The tumors of the testicle, which are frequently classified in the literature as sarcomas, but which are more often either embryonal or mature carcinomas, have long been believed by some writers to be caused by trauma. Of the two types of testicular carcinoma, one arises from embryonal remnants present long before adult life, and the other, the adult carcinoma, or seminoma, arises from the germinal epithelium. Only with regard to the latter should there be any question of traumatic origin. Both types—the embryonal and the mature—grow rapidly, so that a blow one year before may not in any case be considered a cause. As has just been said, all the tumors

64 Ribbert. *Deutsche med. Wchnschr.* **21** 9, 1895.

65 Lepine. *Lyon med.* **100** 18, 1903.

66 Sattler, H. *Die bosartigen Geschwulste des Auges*, Leipzig, 1926.

67 Wintersteiner, quoted in Lubarsch-Ostertag. *Ergebn. der allg. Path. u. path. Anat.* *Erganzungsband* **10** 1044, 1907.

which can be shown to be teratoid should be excluded from the traumatic group. Some surgeons do not take this position, however, for instance, Coley,<sup>68</sup> who believed that a large percentage of the complex teratoid tumors were traumatic.

Virchow believed that tumors arose in the undescended testis more frequently than in the normal one, and ascribed the difference to chronic irritation. This greater frequency was affirmed by some, and denied by other recent writers (Bulkley<sup>69</sup>), who did not consider trauma as of any importance but believed it either caused hemorrhage in an already existing tumor and hence called attention to the growth or stimulated a tumor to increased activity. Many other writers have followed Siegfried Wolff,<sup>70</sup> who thought that as traumatic tumors they were second in frequency only to the bone tumors.

Brunne<sup>70</sup> collected thirty-five cases, in thirty-four of which there was record of injury to the testis, but described only one in which evidence existed that a normal gland had been present prior to the injury.

Weinert<sup>71</sup> reported a case of a trauma of the right testicle followed by an increase in size of the gland. Extensive metastases quickly caused the death of the patient. The tumor was a large cell sarcoma (seminoma), and Weinert thought that a causal relationship could not be traced between the trauma and the neoplasm.

*Sarcoma*—The most important and perplexing portion of the discussion has centered around the question of the relation of cases of sarcoma of the bone and of fascial sarcoma to trauma. All the groups were included in the long reviews mentioned, but the percentage of cases thought to be due to trauma will not be given here because of the obvious discrepancies in the observations of different writers and the fact that their work has not been subjected to critical analysis. Ribbert<sup>74</sup> stated that occasionally single cases were difficult to explain, but he willingly denied any general relationship. A case described by Ott<sup>72</sup> is of interest. A boy, 2½ years of age, was bitten by a dog on the forearm. The lesion continued unhealed for four weeks. The scar became much thickened in three months, after which an ulcer was excised. This was said to be a small round cell sarcoma, but no type of malignant tumor is more readily confounded with chronic inflammation, for example, syphilis. How difficult it may be to make such a

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68 Coley, W. B. *Ann Surg* **76** 370, 1923.

69 Bulkley. *Surg Gynec Obst* **17** 703, 1913.

70 Brunne. *Ein Fall von Hodensarkom auf traumatische Basis*, Diss., Greifswald, 1903.

71 Weinert. *Handbuch der aertzlichen Erfahrungen im Weltkriege*, Leipzig, 1921, p. 51.

72 Ott. *Munchen med Wchnschr* **57** 103, 1901.

morphologic differentiation, is illustrated by an amputation done at the instance of a well trained pathologist who could not differentiate on a biopsy between round cell sarcoma and syphilis. Clinically the condition resembled sarcoma. Many descriptions of allegedly traumatic cases, unaccompanied by a microscopic section, an x-ray photograph or a statement of the clinical outcome, fall into the anecdotal group, they cannot be accepted as having as much probability as some of the cases of bone sarcoma, which are more completely described and the microscopic diagnosis of which cannot be challenged. Graef<sup>77</sup> believed that sarcoma more frequently followed the crushing injuries, both moderate and severe, but not open wounds. Ewing<sup>10</sup> asserted that neurogenic sarcoma is never traumatic in origin, but has a congenital basis. The osteogenic spindle cell type of tumor he regarded differently, he described such a growth which arose over the patella after a fall on the knee, and caused complete disability and constant symptoms until death six months later. In so important a tendon as that of the quadriceps, the question of a preexisting tumor being responsible for the fall cannot be excluded on the basis of the case report.

The three lengthy articles by Coley<sup>73</sup> on bone sarcoma and other types of malignant tumor, in which he stated that of 270 cases of sarcoma personally observed, 60, or 31 per cent, and of 800 subsequent cases, including 61 different types of cancer, 179, or 23 per cent of the whole group were associated with trauma, do not, after careful reading, in my opinion, justify the conclusion that the trauma was associated in a causal relationship. That the trauma was antecedent is all that can be concluded. Coley discussed a large group of these cases, which he said must properly be called cases of "acute traumatic malignancy," but the meaning of such a term, although used at one time especially by the English, is somewhat ambiguous, and the tumors, which appeared within a week, cannot be understood to have been caused by trauma. The conclusions in the three papers are essentially the same.

Mock and Ellis,<sup>20</sup> as well as others, thought that "not more than half of these cases were even fairly convincing." Coley himself selected six which he thought could not fail to convince the most skeptical, and these are, in fact, the only ones which are not open to serious doubt.

Kolodny<sup>74</sup> pointed out that the trend of modern thought with regard to bone sarcomas, as with other types of malignancy, is to look for many causes, not one only. He agreed that trauma was "frequently

73 Coley, W. B. *Ann Surg* **27** 259, 1898, *ibid* **53** 449 and 615, 1911, *M News* **78** 575, 1901.

74 Kolodny. *Bone Sarcoma, Surg Gynec Obst (suppl 1)* **44** 5, 1927.



associated with the origin of bone sarcoma" and pointed out the similarity of some bone tumors to callus formation in vascularity, cell morphology and clinical appearances. Although conceding these points, he gave the reverse side of the discussion full weight, that is, the rarity with which a trauma produces a tumor suggests that the single trauma is not even an adjuvant etiologic factor, and that there is a more profound predisposing factor in the persons who have tumors.

The case described by Amberger<sup>75</sup> is not difficult to understand, it illustrates, however, a type of tumor which, because of its obscure position, is often regarded as having an obscure cause. His patient, a young man of 19, in good health, had sustained a fall on one of his buttocks on the ice. This was followed by severe pain in the buttock. An accompanying injury of his scalp kept him in the hospital for three weeks. X-ray photographs of the painful buttock taken at the time did not show lesions. Three weeks afterward, the pain involved the sciatic nerve, and six weeks after the injury, a swelling in the buttock could be noted. A microscopic examination of the tumor was not made. At the end of the next three months, the patient died with an enormous tumor and generalized metastases.

Many cases of tumor of the pelvic bones similar to this one have taken much longer than this did to appear on the surface. Furthermore, the x-ray photographs often have not revealed abnormal conditions, despite the presence of a growth for a much longer period than that covered by the x-ray examinations. It is too often forgotten that an extensive neoplastic growth may surround a bone and give no demonstrable shadow until bone absorption begins. This solution of the bone substance may be delayed for a long time. The tumor in Amberger's case eventually involved the iliac bone but could not under any circumstances have been detected by palpation or x-ray in the beginning. It seems much more probable that the muscular control necessary in skating was disturbed by the presence of the tumor and that this caused the original fall through a loss of balance. Had the patient not fallen, the tumor might not have come to his observation until a few weeks or months later. The fall added to the disability of the patient, but it did not by any means offer proof that it had caused the tumor.

Haberein,<sup>76</sup> in 1892, collected and discussed cases of the so-called callus sarcoma, when reporting his own case, he quoted Biuns to the effect that the descriptions of the sixteen cases in the literature were lacking in both anatomic and microscopic details. Haberein's case was that of a man of 54, who fell under a heavy wagon, which passed

75 Amberger *Monatschr f Unfallh* **17** 69, 1910

76 Haberein *Arch f klin Chir* **43** 352, 1892

across his chest and the left humerus, causing a comminuted fracture of the latter above the condyles. This was put in a splint for six weeks. It was then regarded as normally healed and was treated with baking and massage. The patient was not seen again for nine months. At the end of this time he returned with a large, painful osteochondrosarcoma at the site of the old fracture. This had been growing for two months. This case appears to have been carefully scrutinized, with the exception that roentgenographic studies were not made. It is of more interest than most of the published examples, because of the history of violence applied directly at the site, the period of observation after the fracture and the microscopic examination in which the growth was clearly described as malignant.

Of these cases of various types of sarcoma the last case illustrates the real problem, for in it one sees that, though the clinical records seem convincing, there must always remain the possible explanation of a small, unrecognized, previously existing tumor, in view of the enormous number of fractures occurring annually, following which neoplasms do not arise.

*Tumors of the Brain*—Even writers who did not admit the traumatic origin of bone tumors, were inclined to acknowledge a probability that some of the cases of glioma reported were related to cerebral injuries, von Hansemann,<sup>5</sup> Duick<sup>77</sup> and Reinhardt<sup>78</sup> were among the number. It must be accepted, however, that glioma offers the greatest difficulty because it is even more completely concealed from observation, and in the cases detailed in the literature the injuries described by the patients occurred at a much earlier period than the traumas in the other types of neoplasm alleged to be due to trauma. There are great variations in the statistics on this subject. The long compilation by Adler,<sup>79</sup> consisting of 1,086 cases, from which he derived the conviction that 88 per cent were related to trauma, presents many difficulties to a critical reader, as the injuries described do not appear to show any important connections between the trauma and the tumor, also distinction is not made between types of cerebral tumors.

Modern methods of histologic technic have shown that the gliomas form a complex group and that there is always danger of confusing certain types of proliferative gliosis with true neoplasms.

Gerhardt,<sup>80</sup> in a series of sixty cases, ascribed 17 per cent to traumas, and Monakow,<sup>81</sup> in a series of forty-one cases, believed that 24 per cent

77 Durck, H. *Klin Wchnschr* **3** 658, 1924.

78 Reinhardt, G. *Munchen med Wchnschr* **75** 399, 1928.

79 Adler. *Arch f Unfall* **2** 189, 1897.

80 Gerhardt. *Das Gliom*, Wurzbürger Festschrift, 1882, vol. 2.

81 Monakow. *Schweiz Arch f Neurol u Psychiat* **14** 289, 1924.

were traumatic Hubschmann<sup>82</sup> believed that in a series of 107 cases, 75 per cent were probably, though not certainly, traumatic Reinhardt,<sup>78</sup> on the basis of war injuries, said that tumors of the brain had not increased and that therefore the inference of a traumatic cause for them was to be denied Neuburger,<sup>83</sup> however, described two cases of glioma each of which followed six years after a cerebral injury sustained in the war Nevertheless, he was unable to show that the gliomas had not arisen on a basis of chronic irritation of the supporting substance of the brain, as extensive chronic connective lesions were also present He acknowledged that a special cellular disposition of the brain of the patient must have been concurrently present, as most cerebral injuries of the same type do not give rise to gliomas

Reinhardt<sup>78</sup> believed that in order to establish that a tumor of the brain or the meninges was caused by a trauma it must be shown that the tissues had been lacerated, that between the trauma and the first symptoms of the tumor there had been at least several weeks without symptoms and that the tumor is at the point of injury, further, the morphology and histogenesis of the tumor must be definitely stated

An interesting case was described by Reinhardt, in which a gliosarcoma occupied a portion of a frontal lobe in a patient who had sustained an injury due to a foreign body, which apparently had entered the orbit and embedded itself in the frontal lobe twenty years before The foreign body was a metallic fragment, 1 cm by 0.33 cm, and it was removed from the tumor at autopsy The gliosarcoma can scarcely be alleged to have arisen from a single trauma, but rather from a chronic irritation

The frequently quoted cases described by Becker,<sup>84</sup> who questioned many of the uncritical statistics in the literature, added only another to the improperly included cases The recorded history should be accepted only as an example of the utterly unscientific and untruthful accounts which obscure the literature The patient, a coachman for the physician who observed the case, suffered a severe contusion of the head from an accident in which his horses were suddenly startled and he was thrown to the ground Afterward deafness slowly developed in the left ear, so that the physician was obliged to shift his position to the right side of his driver Nausea, vertigo and altered personality followed in due course The man died A gliosarcoma was disclosed at autopsy The astonishing observation was made by the physician that although the patient had been suffering from frequent headaches prior to the blow on the head, he did not think that the tumor of the brain had been already established, since the man had been able to pursue his regular work

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82 Hubschmann *Deutsche Ztschr f Nervenhe* **66** 1, 1920

83 Neuburger, K *Munchen med Wchnschr* **72** 508, 1925

84 Becker *Aerztl Sachverst-Ztg* **16** 153, 1910

The single case reported by Richter,<sup>85</sup> in which an endothelioma of the dura developed on the inside of the skull of a man who thirty-eight years before had been injured by the fall of an iron kitchen utensil and rendered unconscious for fourteen days, is highly circumstantial

Ewing did not accept the traumatic origin of endothelioma nor did he believe that glial cells regenerate easily. He stated that most of the tumors of the nervous system are referable to disturbances in the structural development of the ectoderm

Von Hansemann<sup>5</sup> thought that gliomas are altogether too few when compared with the large number of injuries of the head to make their occurrence of any importance as a causative agent. He also stated that a latent tumor may suddenly give symptoms if an unusual movement such as bending or straining causes the spaces and vessels of the tumor to become engorged

It is therefore the tendency of the more recent writers to question seriously a traumatic origin for glioma as for the other types of tumor and to feel that logically there is no reason to connect whatever injuries may have been sustained by the head years before with the presence of a primary tumor of the brain

#### EFFECTS OF TRAUMA ON A PREEXISTENT TUMOR

The general subject of what may be expected to be the effect of a trauma on a preexisting tumor is important, as, unquestionably positive results will be presupposed in every case by the lay mind, and many of these cannot be scientifically excluded. Lubarsch believed that changes in a preexisting tumor could be attributed to a tumor only if the injury was such as to cause a change in the metabolism of the cells, and such as to increase the rate of growth of the cells, and if histologic investigation of the trauma showed the results of hemorrhage, that is, phagocytosed blood pigment and altered vessels. Lubarsch, however, recognized the fact that untraumatized tumors do not grow with any regularity and that considerable periods of rest may alternate with active periods of growth, a phenomenon which has been abundantly studied in the tumors of animals (Woglom<sup>86</sup>). This is a factor dependent to a considerable extent on the biology of the individual tumor, for certain tumors, such as vascular hypernephromas, apparently enlarge rapidly for a time, but spontaneous hemorrhages are frequent, and following these, regressions—probably due to thrombosis and hemorrhage—are frequent. Other tumors of the more fixed, scirrhous type, such as many of the carcinomas of the breast and the adenocarcinomas of the sigmoid, are

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85 Richter, H. *Klin Wchnschr* 5 1617, 1926

86 Woglom, W. H. *The Study of Experimental Cancer*, New York, Columbia University Press, 1913

relatively avascular, and do not fluctuate in size. It is difficult to produce hemorrhage in them even by direct traumatization, they are scarcely ever found to be hemorrhagic at operation, except when massage or manipulation has been carried out immediately before, and even then only the superficial portions of the tumor are ever seen to be affected and they but slightly. It cannot be denied that a tumor, for instance of the recto-sigmoid junction, already adherent to the sacrum might be slightly detached from the bone, or that sufficient traumatization might occur over the periosteum through a direct blow or a hard fall to cause increased pain in the tumor. There is also the possibility that a pedunculated tumor might become acutely painful following a fall or a blow because of torsion of a peduncle with attendant hemorrhagic infarction, and thus attract the patient's attention. A pedunculated myoma of the small intestine of an extremely vascular type has been known to perforate through the serous covering at the moment when the patient lay down for examination and before any pressure had been exerted on the abdomen. Should this occur coincidentally with any external violence, the perforation would be attributed by the patient to the trauma. Unquestionably, sufficient traumatization might hasten such a perforation.

A trauma may, also, by depressing the vitality of the tissues, favor the localization of infection in a tumor, and lead to subsequent suppuration. Necrosis and even gangrene might occur as a result of a sufficiently severe trauma applied to certain portions of a tumor if it involved a peduncle or the major portion of the blood supply. Infection may frequently cause regression in the size of a tumor by giving rise to numerous thromboses, and this is especially true in the case of lymphangiomas and other tumors which may become infected with the streptococci. The streptococcus of erysipelas is especially likely to cause thrombosis of thin-walled capillaries. Von Hansemann believed that trauma might accelerate growth. That this is not a necessary result of the trauma, however, was shown by Rohdenburg,<sup>87</sup> who collected instances of the partial removal of tumors which did not show accelerated growth resulting, and which did show disappearance for a long period. The experiments carried out by Wood,<sup>88</sup> in which biopsies were performed on carcinomas transplanted in mice, failed to show acceleration of the rate of growth of the tumors following the incisions.

Stern<sup>40</sup> stated that no doubt many tumors grow faster as a result of traumas, but that there cannot be a general rule for this, that perforation of a preexisting carcinoma of the stomach is possible, but that this also cannot be proved to be due to the trauma. There does not seem

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<sup>87</sup> Rohdenburg, G. L. *J. Cancer Research* **3** 193, 1918

<sup>88</sup> Wood, F. C. *Diagnostic Incision of Tumors*, *J. A. M. A.* **73** 764 (Sept. 6) 1919

to be any doubt that sarcomas of the extremities are frequently aggravated, symptomatically at least, by superficial injuries. Periosteal lesions are notably painful ones, and a blow severe enough to cause hemorrhage in the periosteal covering of a tumor or in the superficial parts of a tumor derived from the periosteal layers of the bone no doubt aggravates the symptoms endured by the patient and fixes his attention on the lesion. It is quite possible that a moderate traumatization of the skull might cause an extensive hemorrhage in a tumor of the brain and thus reveal a hitherto unsuspected neoplasm. It is conceivable, also, that the cellular portion of such a growth might be in some cases temporarily stimulated by the congestion or vascularity resulting from hemorrhage and by the subsequent repairing which may be the consequence of the trauma, but the opposite possibility must be kept in mind, which is that necrosis of a portion of the tumor and subsequent shrinkage may also be directly due to the injury.

The gastro-intestinal tract can sustain lacerated wounds as the result of external injury, especially the anterior coils of the small intestine (Vance<sup>89</sup>). More rarely one of the other portions of the intestine or of the colon may be ruptured. The duodenum or the colon may be contused severely enough to cause tears, thrombosis and necrosis. If a preexisting tumor of the gastro-intestinal tract is injured in this way, it is conceivable that the tumor cells might be more widely distributed than would otherwise occur. This is true also in the case of a rupture of ovarian or other cysts which contain viable cells, which may become readily implanted on remote peritoneal surfaces. The fixation of the tumor is a most important factor. Organs such as the esophagus, which are entirely inaccessible to outside influence, do not rupture from external violence. Numerous decisions against compensation in cases of carcinoma of the stomach and esophagus were cited by Engel<sup>2</sup>.

Sebestyén,<sup>90</sup> in a recent compilation of 4,068 cases of sarcoma, found that 15 per cent belong to the group of so-called traumatic sarcomas of the bone. He included three of his own cases in which the traumatic influence seemed to him unusually probable. The first was that of an infantryman, aged 23, wounded in the right shoulder in 1916 by a blow from a gun stock. The joint remained painful and swollen with limited motion for two months. There was a venous dilatation over the area, but not any scars. The x-ray showed a thickening of the cortex and a radiating bony deposit extending into the soft parts. Evidence of fracture was not seen. Diagnostic incision showed a spindle cell sarcoma.

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<sup>89</sup> Vance, B. M. Subcutaneous Injuries of Abdominal Viscera. *Anatomic and Clinical Characteristics*, Arch Surg **16** 631 (March) 1928.

<sup>90</sup> Sebestyén, J. Arch f klin Chir **136** 716, 1925.

with osteoid deposits. The patient died two weeks later. An autopsy showed general sarcomatosis with widespread metastases.

The second case was also that of an infantryman, aged 26, wounded in March, 1917, by a blow on the elbow from a stone. Pain was present for two months. Then the outline of the elbow was found to be altered by swelling around the joint. Motion was limited. The x-ray showed radiating bony deposits extending from the coronoid process of the ulna into the soft parts. A diagnostic incision showed an osteochondrosarcoma of the ulna.

The third patient was also a soldier, aged 36, wounded Jan. 20, 1918, in the same way as the soldier in the preceding case except that the wound was open. It healed in three weeks, and he regained use of the arm. Eight months later, when he presented himself, he had a tumor in the middle of the right thigh, a swelling which was hard and attached to the bone and fixed in the surrounding tissue. The x-ray also appeared to show a thickening of the cortex and new spicules of bone extending into the soft parts. Diagnostic incision showed a malignant tumor arising from the connective tissue composed of spindle cells with some osteoid material between them. Sebestyen<sup>90</sup> pointed out that although these tumors seemed to arise from the periosteum, morphologically it was possible that they arose from the endosteum or even from the bony substance itself, and that there is no more difficult task for a pathologist than judging correctly the exact point of origin of a sarcoma of the bone from microscopic sections.

These cases were considered by Sebestyen as of periosteal origin. He concluded that most of the traumatic sarcomas of the bones which follow a single direct injury are clinically of the periosteal type with a short latent period, while those due to open injuries, distortion or fracture and with a longer latent period, are more often sarcomas of the central myeloid type.

Paul Segond<sup>91</sup> discussed the statistical collections of case reports of tumors of alleged traumatic origin, and doubted that they have any value, quoting Auguste Comté to the effect that they represent only "empiricism under a mathematical disguise, for the most extensive statistics when they are derived from a variety of sources often have less value than fifteen minutes of good observation." Consequently, all that could be said, he thought, was that a tumor is produced by a trauma only rarely and then probably by the intermedium of a chronic process. He granted that even this intermedium is "easy to argue about and difficult to prove." He then went on to study a series of conditions somewhat aside from the main theme under discussion, but of general interest. He considered, for example, a person who already has a cancer

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91 Segond. *Ass. franç. d. chir.* 20:745, 1907.

who receives a blow at a point distant from the cancer. Owing to his poor condition, the injury may be more serious than it would be to one in perfect health, and the question of some compensation may have to be considered. Again the blow may strike the tumor and aggravate it, or a spontaneous fracture sustained by a person while employed may be found to be due to a sarcoma of the bone. In a case cited, the French courts refused compensation, holding that the disease which caused the fracture did not have any relation to his work. Another situation arises when a person who has a scar, fistula, ulcer or old callus is injured at the site of such lesion, and ultimately develops a tumor there. In commenting on these three instances, Segond made mention of "attenuated liability." Finally, the question of compensation arises when the trauma produces a scar, fistula, ulcer or callus which much later and spontaneously becomes the site of a tumor. Under these circumstances, the trauma is certainly not a causative agent, but rather the patient's underlying constitution is, this is a vague notion, perhaps, but one expressing what every one recognizes. In most people, a cancer does not develop in a scar or in an ulcer, but rarely a malignant growth does appear. This difference in persons must be ascribed, pending further knowledge, to some peculiarity of the individual structure of the person. Such susceptibility to formation of tumors has been demonstrated in animals and is probable in man. Of its nature nothing is known. Compensation for this situation can scarcely be thought of.

The possibility that benign tumors may be converted into malignant ones under the influence of trauma is apparently remote, although a few types are believed to be more commonly susceptible to such a transformation than are the rest. It is doubtful whether an acute trauma has ever accomplished such a change. There is no doubt, on the other hand that irritation of a chronic type applied to keratoses to certain adenomatous tumors, such as polyps of the intestine, and perhaps to quiescent nevi, is often effective in bringing about such a change. Few pathologists, however, believe that circulatory changes lasting a few weeks, such as the exudation about a sprained joint, a carbuncle or a hematoma, is sufficient chronic irritation to produce a tumor. The irritation must be prolonged.

Frangenheim<sup>55</sup> was among those who believed that some tumors are changed from benign to malignant ones by outside irritants. Ewing<sup>30</sup> stated definitely that a single trauma had never in his observation changed a benign quiescent remnant of tumor cells into a malignant tumor. Such a statement would include the nevi, the hypernephromas, the mixed tumors of the salivary glands, the branchiogenic cysts and the neurofibromas. The case of Versé,<sup>92</sup> who described an extensive neuro-



fibromatosis occurring in father and son, puts undue emphasis on the trauma sustained by the father who injured one tumor on his foot. This tumor was excised but recurred in three years. In six years, a tumor appeared on the scalp, and the patient shortly died with neurosarcomatous metastases. It is impossible to attach much importance to the original trauma when the course of the case makes it obvious that the tumors were capable of becoming malignant without the trauma. Von Hansemann<sup>93</sup> discredited the importance of irritation of nevi, stating that they are normally insensitive and hence are only scratched or rubbed by the patient after the malignant process has already begun.

*Metastases*—It has been proved (Knox<sup>94</sup>) that repeated pressure in examination or massage may cause wide distribution of particles of a tumor, whether a single blow can accomplish the same is not known.

The question of the localization of metastases through trauma has been widely considered. Brinkmann<sup>95</sup> recently reported a patient with a bone tumor resembling thyroid tissue and supposed to have been localized as the result of a fall. Lubarsch<sup>96</sup> by experiments on mice showed that the localization of metastases, as in the liver, can rarely be determined by a single injury. He also said that this could be assumed to be true only if the localization is in an unusual site and the trauma is sufficiently severe to cause cells of the tumor to enter the veins. He regarded injuries caused by crushing or shaking as the most effective. He further attempted to induce metastases in the bones of mice with inoculated tumors by fracturing one of the long bones, but these experiments were consistently negative. Jones and Rous<sup>97</sup> showed in animals that injury to the peritoneum can permit localization of particles of a tumor. In their opinion the injury causes a rapid reparative process in the subendothelial connective tissue and such rapidly proliferating highly cellular tissue elaborates the supporting and nutritional stroma which facilitates the growth of the tumor cells. This may also be valid in other situations.

#### SUMMARY AND COMMENT

The question of the traumatic etiology of tumors therefore appears to have been largely excluded by most pathologists so far as is meant a direct exciting and essential cause. Von Hansemann,<sup>93</sup> Gruber<sup>98</sup> and Pick<sup>31</sup> pointed out that after all the injuries sustained in the war no greater number of tumors could be observed in the war veterans, even

93 Von Hansemann. Handbuch der Aertzlichen Erfahrungen im Weltkriege, 1921, vol 8 p 53

94 Knox, L C. Ann Surg **75**:129, 1922

95 Brinkmann, E. Klin Wchnschr **6** 1903, 1927

96 Lubarsch. Med Klin **8** 1651, 1912

97 Jones, F S, and Rous, Peyton. J Exper Med **20** 404, 1914

98 Gruber. Ztschr f urol Chir **13** 66, 1923

in those who were of an age at which sarcoma most frequently occurs, than in civilians. Ten years have now elapsed, and an increase in the incidence of tumors has not been noted in the population of any of the combatant nations.

Pick<sup>31</sup> especially regarded his opportunity with the army of the western front as affording a mass of homogeneous experimental material and believed that if sarcoma could result from external injury he should see many cases in his service at that time, since the age of the soldiers corresponded with the period of frequency of sarcoma. Only two cases of sarcoma appeared which he could even suspect of arising from war injuries.

In 1918, the French Association for the Study of Cancer was requested to report on the relationship between traumas and tumors in the light of the experience obtained during the war. A number of important pathologists and clinicians discussed the problem and practically all except Bérard thought that traumas had practically nothing to do with the appearance of tumors. Bérard<sup>4</sup> had already reported favorably on the possibility of such an influence.

Forgue<sup>99</sup> showed that the regional distribution and the age distribution in 536 cases of cancer were practically proportional to the like distribution in the male population not in the service.

Von Hansemann,<sup>93</sup> also, pointed out that not only has an increase in tumors not appeared following the war, but new types have not appeared.

Lowenstein,<sup>100</sup> in his military service extending from 1889 to 1917, also calculated that among the young men whom he had observed the percentage of sarcoma arising in such a group should be 12 per cent, but he was unable to report any such percentage.

Eunike,<sup>101</sup> also, observed six examples of sarcoma of the bone which he believed might possibly be due each to a single trauma, but stated that the rarity of such lesions shows that other influences are essential to their production. His paper is one of the best on the subject, and shows judicial handling of a series of interesting and carefully studied individual cases.

Brosch<sup>102</sup> stated that a single trauma preceding a pathologic process could not cause a tumor, but that the early productive and reparative changes observed in scars were essential forerunners of the neoplastic process and that this accounted for the inability of experimenting pathologists to produce tumors in normal tissues.

99 Forgue. *Bull d'ass franç p l'étude du cancer* 7 555, 1914-1918

100 Lowenstein, quoted from L. Pick. *Med Klin* 17 416, 1921

101 Eunike, K. W. *Deutsche Ztschr f Chir* 151 262, 1919

102 Brosch, A. *Virchows Arch f path Anat* 162 32, 1900

Goebel<sup>103</sup> also stated frankly that a single injury never caused a malignant tumor, but that chronic irritation, repeated injuries and scar tissues indirectly, but not entirely mechanically, might have done so. The thermal and chemical reactions consequent to the other pathologic processes were essential. Oberndorfer<sup>104</sup> also asserted dogmatically that trauma could not independently cause proliferation of normal cells, that some underlying predisposition must be present.

Frangenheim<sup>55</sup> was inclined to believe that trauma might have had some relation in some cases but that it could not be a primary or chief cause because of the large number of tumors in new-born infants and other infants who had not suffered traumas.

Virchow,<sup>105</sup> also, while admitting the fact that the influence of trauma could not be dogmatically denied, required that there should be some as yet unknown predisposing factor in the patient and also that the trauma must have been implanted on pathologic tissues.

Ribbert<sup>24</sup> consistently opposed the theory that a trauma could cause a tumor but admitted that, although positive proof was lacking, the possibility must be conceded. He denied ever having seen a clearly demonstrated case.

Jordan,<sup>106</sup> in discussing the origin of tumors from single traumas, held that "in regard to the current hypotheses of tumor formation following injury we possess no information concerning the actual rôle played by trauma." Further, he pointed out that the time required for the development of a tumor is in general unknown and he called attention to the fact that after the extirpation of a carcinoma many years might elapse before metastases make their appearance. Again he stated that as tumors arise from small groups of cells "we are never in a position to deny that a small tumor may have preceded the trauma which is alleged to have caused it." Nevertheless, he granted that in the law "possibilities and probabilities" have to be considered and that compensation might be proper when the injury had caused a hitherto unrecognized tumor to grow rapidly and thus become evident.

Theilhaber,<sup>107</sup> whose conclusions in general were compiled without critical study, convinced himself of the importance of atrophied scars as a prerequisite to the formation of tumor tissue. This is one of the hypotheses which can apply only to small groups of tumors in any case.

103 Goebel *Sammlung klinische Vorträge*, Leipzig, 1905 p 403, *Chirurgie*, no 110, 209

104 Oberndorfer *Aerztl Sachverst-Ztg* **13** 32, 1907

105 Virchow *Die Krankhaften Geschwulste*, Berlin, 1863

106 Jordan *München med Wchnschr* **48** 1741, 1901

107 Theilhaber, A *Deutsche Ztschr f Chir* **110** 77, 1911 for complete bibliography of writer's own publications see *Die Entstehung und Behandlung der Karzinome*, Berlin, 1914

and has little bearing on the question of acute trauma, as no one supposes that sarcomas of the bones in young people have any relation to old scars in the periosteum or bone

Versé,<sup>92</sup> also, stated that there must be a general and a local disposition to the formation of tumor, a statement so general as to afford one little conception of what is meant

Sauerbruch<sup>46</sup> and Ewing<sup>30</sup> were both of the opinion that the anatomic flexures, angles and points of greatest mechanical and chemical stress are the ones in which tumors are most likely to develop—this again being a generalization scarcely related to the subject since the trauma referred to is repeated and persistent

Borst<sup>108</sup> did not feel that trauma could be entirely excluded, because of the difficulty of explaining obscure cases. But why explain the inexplicable by a new hypothesis? He by no means accepted traumas, however, as a general cause of tumors, but like Pick,<sup>31</sup> Eunike<sup>101</sup> and Ewing<sup>30</sup> was willing to admit the possibility of occasional cases differing from the rest

Hauser and Beneke,<sup>109</sup> also, noted that the distribution of tumors in general showed that traumas could not be the only cause, for example, the large number of malignant tumors of the breast as compared with the small number in the extremities, where trauma, it is admitted by all, is sustained the more frequently. Roger Williams<sup>110</sup> regarded this as an important argument against the traumatic theory, and declared that men sustain three times as many injuries to the breast as women, but that they suffer from carcinoma of the breast in the proportion of one man to 116 women

It is therefore evident that any critical observer influenced by the leaders in pathologic thought will hardly consider trauma to be a general cause of any type of tumor. Some pathologists, as has been pointed out, admit it as one of the factors which might act at a favorable moment in an individual with some local or general susceptibility to tumor, and so be an important contributory cause. Even as to this, Williams was emphatic in asserting that if trauma were a contributory cause one should see more cases of multiple neoplasms, since the soil on which the injuries of life were being inflicted was a proper one. The bilateral varicose carcinomas of the extremities are an instance of the importance of the individual predisposition when combined with a chronic irritant. Most observers believe the trauma to be only an external factor calling attention to a preexisting or subsequent but independently caused tumor

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108 Borst, quoted by Ziegler (footnote 33)

109 Hauser and Beneke, quoted by Ziegler (footnote 33)

110 Williams, Roger. *The Natural History of Cancer*, New York, 1908, p. 286

The frequency of such unrecognized cancer has been clearly brought out by Wells,<sup>111</sup> who showed that as the diagnostic error in cases of cancer as revealed by necropsies in various hospitals is from 25 to 40 per cent, the percentage of error in diagnosis among the population at large must be much greater. Probably 50 per cent of the neoplasms in some communities are never diagnosed. It is evident that with so large a group of persons whose cancers never are recognized, there are ample opportunities for an accidental trauma to be considered as a causative agent. If the current reported death rate from cancer in the United States is taken as about ninety per hundred thousand, the unrecognized cases can scarcely be less than forty, as but proportionately few autopsies are performed in this country. This makes the true death rate probably 130 per hundred thousand, or about that of Switzerland, where a large proportion of those dying are given postmortem examination. As the average life of a patient with cancer has been computed to be about two years, there should be in the population as a whole some 250 persons to the hundred thousand who have cancer in some stage, in addition to those who are to die within the year and are so recorded. In other words, besides those evidently dying of the disease, one person in 400 of the whole population may have a cancer in some stage of development. As sarcoma forms about one tenth of the total number of malignant growths, one person in 4,000 may have such an unrecognized sarcoma. The opportunity for a trauma to call attention to such a condition is evidently considerable and must be recognized in any study of the relationship between injury and the production of a sarcoma. This is the type of tumor which the majority of those who believe in the traumatic origin of malignant growths consider to be most frequently produced by injury.

Lewy<sup>112</sup> also showed from the records of the New York State Industrial Compensation Bureau that the frequency of malignant tumors among injured persons was about one to 700, or approximately that of the general population at the age of 50.

Another basis for exclusion of the theory is the statement made by Williams<sup>110</sup> that men are more subject than women to trauma, and this is no doubt true for the more severe injuries, such as fractures, sprains and dislocations. In his material, men have fewer cases of malignant cancer than women, in the proportion of 1 to 17. The difference in these figures is chiefly due to the frequency of carcinoma of the internal organs and not to sarcoma alone and so it is not such an effective argument as it first appears.

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111 Wells, H. G. Relation of Clinical to Necropsy Diagnosis in Cancer and Value of Existing Cancer Statistics, *J. A. M. A.* 80 737 (March 17) 1923.

112 Lewy, R. New York State Department of Labor Med. Bull. no. 1, 1923.

Perhaps a better practical summary of the facts has not been made than that by Lubarsch,<sup>7</sup> who on the basis of wide pathologic experience reminded us

1 That blows and other injuries generally call attention to hitherto unsuspected tumors, and that proof of the existence of such unsuspected growths is given by the fact that neoplasms which have never given recognizable symptoms are constantly being discovered at autopsies

2 That injuries are infinitely more frequent than neoplasms

3 That many tumors have a long latent period

4 That experimental evidence for the theory that a single trauma can cause a tumor is lacking

#### CONCLUSIONS

1 A careful perusal of the more important literature on the relationship of a single trauma to a tumor leads inevitably to the conclusion that a causative relationship between the two has never been completely established

2 A few examples, such as have been cited in this paper as worthy of note, suggest the possibility that a single trauma may induce a tumor, though only in a limited number of situations, but proof even of these few instances is lacking

3 This causative relationship never can be established until it is demonstrated by experimental methods that a single injury can regularly produce a tumor

4 The award of compensation solely on the basis of the production of a tumor following a single trauma is, therefore, unjustifiable

5 The award of compensation on the basis of a trauma acting as a collateral or adjuvant agent by causing chronic irritation which in time produces a tumor, or on the basis of a fracture or other injury in a bone already involved by cancer, or on the basis of violence determining a metastatic site for a cancer already present in the body, or, in exceptional instances, stimulating a tumor to greater activity of growth, may be justifiable if proof of the injury is received and proof of the presence of a tumor is made by the microscope

6 Many of the recorded cases in which compensation has been awarded are instances of trauma merely calling attention to a pre-existing tumor, either in the skeleton or in the organs or the connective tissues. And in the mere presence of such a tumor a valid basis for compensation does not exist. The frequency of such preexisting and unrecognized tumors is shown by the fact that routine postmortem examinations increase by at least one fourth the percentage of cancer found by diagnosis on the living patients in institutions offering the best diagnostic facilities

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## Notes and News

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**Chicago Meeting of Pathologists and Bacteriologists**—The annual meetings of the American Association of Pathologists and Bacteriologists and the affiliated societies, namely the American Association of Immunologists, the American Association for Cancer Research and the Medical Museums Association, will be held in the new laboratory of pathology of the medical school of the University of Chicago on March 27, 28 and 29, 1929. This new laboratory building has been occupied by the department of pathology of the University of Chicago since Oct 1, 1927, and constitutes the center section of the new medical group of the University of Chicago. As shown in the accompanying illustration, it is



New laboratory of pathology, University of Chicago

a connecting building between the medical clinic and the surgical clinic, and forms the central portion of the south side of Medical School Court, thus making it the central part of both the hospital and the preclinical laboratories. It contains 886,000 cubic feet, with 56,412 square feet of floor space, distributed in six floors and a basement. There are twenty private rooms for research workers, as well as five larger laboratories for research work, in addition to three laboratories for class work, three class rooms, a large lecture room, an autopsy amphitheater, and two smaller autopsy rooms, a display museum, a storage museum, a large medical library reading room and numerous storage, preparation and office rooms. The entire upper floor is occupied by animal quarters. The laboratories are entirely for the use of the department of pathology, hospital and clinical laboratory work being done in the clinic buildings. Part of the work of the Otho S. A. Sprague Memorial Institute is also conducted in this building, in conjunction with the department of pathology.



**Cooperative Blood Donor Bureau in New York**—Through the activities of the committee on blood groups of the National Research Council, a committee of interested persons, under the chairmanship of Dr Arthur F Coca, has established a central agency under cooperative supervision for supplying blood donors to hospitals in New York City. At present, the bureau, which is practically self supporting, is serving about twenty hospitals. It is planned to form a corporation, consisting of the superintendents of the hospitals concerned, to manage the bureau, which will be conducted under the immediate supervision of physicians connected with the cooperating hospitals. The Board of Health of New York City has taken under consideration the formation of regulations for the control of agencies supplying blood donors.

**International Nomenclature of Blood Groups**—In 1927, the American Association of Immunologists recommended the general adoption of the designation of the human blood groups by letters as suggested by Carl Landsteiner, who discovered blood grouping in 1900. In the order of frequency of the groups in this country and Europe, these designations are O, universal donor, A, formerly group II, B, formerly group III, AB, universal recipient. The designations represent iso-agglutinogens A and B. This nomenclature is coming into use everywhere, more and more, it has been approved by the committee on hygiene of the League of Nations and is official in the United States Army and Navy. The ARCHIVES requires its use in the papers and abstracts it publishes concerning the blood groups.

## Obituaries

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ALEXANDER A MAXIMOW, M D  
1874-1928

Alexander Maximow was born Jan 22, 1874, in St Petersburg, Russia. From 1882 until 1891, he attended the German gymnasium of Karl May, he graduated in 1891. In the same year he entered the Imperial Military Medical Academy at St Petersburg. Here, as a student, he showed a keen interest in morphologic problems. For his work on the experimental production of amyloid he was given a gold medal by the academy. He passed the examination of this institution in 1896, with special honors. The next three years he spent in the department of pathology. In 1899, after defending his thesis "On the Question of the Pathological Regeneration of the Testis," the degree of M D was conferred on him by the academy. The years 1900 and 1901 he spent in Germany studying, first, he studied embryology under Heitwig in Berlin, he then went to Ziegler in Freiburg, where he completed the first of his classic studies on inflammation. On his return to St Petersburg, in 1902, he was made Privat-Dozent in pathology, and in the following year he was chosen professor of histology and embryology. He held this position until 1922, when he left Russia and came to the University of Chicago as professor of anatomy. This chair he occupied until his death from angina pectoris on Dec 4 1928.

In keeping with his international reputation, he was a member of many scientific societies in this country and abroad.

His scientific work may be divided into four periods. During the first part of his scientific career, from 1896 to 1902, he published a series of papers on normal and on pathologic histologic questions. Some of these were purely descriptive—as on the histogenesis of the placenta—while others were of a more experimental nature. Among these were his studies on experimental amyloid, tissue emboli in the pulmonary arteries, on the pathologic regeneration of the testis and ovary and on the structure of, and the changes in, the salivary gland during secretion. These formed the fundamental, morphologic background of his future work.

The second period included a series of experimental investigations on the histogenesis of the connective tissue in inflammation. In the first of these, he classified the various cells in inflamed tissues and traced them to definite cell types of the normal connective tissue and blood. With great clearness, he elucidated the rôle played by the hematogenous



(Photograph supplied by Helen R Webster studio)

ALEXANDER A MAXIMOW, M D

1874-1928



and histogenous lymphoid elements in the production of the mononuclear exudate cells—which he called polyblasts—and later in the formation of the scar. He showed that the polyblasts were endowed with a much greater vitality and capacity for progressive development than had been known before his work. The results of this first monograph were developed and completed in a series of subsequent papers. At this time, he also published careful histologic analyses of the cells of the normal connective tissue.

The third period of his work can be looked on as a natural extension and expansion of the second period. From his previous studies he realized that a close relationship existed between the cells of the connective tissue and those of the blood. But the nature of these relationships was not clear, because of the confusion then reigning in morphologic hematology. He realized that the histologic investigation of the adult organism alone could not lead to a decisive solution of these problems. He accordingly began his classic, histogenetic studies of the embryologic development of the blood and connective tissue. Some of these were published in a series of ten papers under the title of "Studies on Blood and Connective Tissue." In these, the first stages of the embryonic development of blood and connective tissue cells and the histogenesis of the bone marrow and thymus were studied in mammals, amphibians and selachians. He also demonstrated the morphologic characteristics and differences of the hematogenous and histogenous mast cells.

In this period, he succeeded, moreover, in proving the development of all blood cells from a common mother cell—which he identified with the lymphocyte—in the kidney, after ligation of the blood vessels of this organ. He thus confirmed the unitarian theory of hematopoiesis, of which he was one of the leading proponents.

The last period of his scientific work was devoted in great part to investigating the prospective potencies, interrelationships and histogenesis of the mammalian blood and connective tissue cells by the method of tissue culture. By using this method, he was able to produce further confirmatory evidence of the fact that lymphocytes of the blood, as well as of lymph nodes, are undifferentiated cells. He was able to observe their transformation into myelocytes and, under different conditions, into polyblasts and later fibroblasts. In his last experiments—of which he had published only preliminary notices—he was able to trace the purely extracellular origin of argyrophile and collagenous fibers in tissue cultures.

In 1927, he published, in von Mollendorff's "Handbuch der Mikroskopischen Anatomie," a very complete monograph on the connective and blood forming tissues. It is richly illustrated by the careful, lifelike

drawings which have made all of his papers valuable, objective contributions to the various subjects he investigated. This monograph also comprises a critical survey of practically the entire literature on this subject and contains excellent summaries of the leading hypotheses, theories and facts in this highly controversial field.

He always spoke of himself as a "simple morphologist" but in the same breath he maintained that there are many problems which as yet, by their very nature, can be investigated only by morphologic methods. He demanded of his students and of the other workers in the fields under investigation an exceedingly high standard of histologic preparations. His own slides were universally acknowledged to be of a superior quality.

The descriptions in all his papers, both verbal and pictorial, are highly objective. He drew the simplest conclusions deducible from his observations. When new facts became established in his own or another's work, he never hesitated to acknowledge his previous errors and to change his theories accordingly if necessary. But, withal he was highly critical, and demanded clea-cut proof from others as well as of himself.

In addition, it must be pointed out that Dr. Maximow was an inspiring, stimulating teacher, particularly to those of us who have had the privilege of working intimately with him in his laboratory. One should also not lose sight of the fact that he was one of the outstanding general histologists of his generation. To this bear witness not only his previously mentioned writings but also his Russian textbook on the "Principles of Histology," in two volumes, and his nearly completed American textbook.

No matter what the future brings in the way of interpretation and elucidation of the many problems investigated by him particularly in the field of the blood and connective tissue, of this much I am sure that the observations of Alexander Maximow made with the best experimental histologic methods of his time, will stand. For many years to come, his work will offer a firm base for further work on questions involving the normal and pathologic histology and histogenesis of the blood and the connective tissue—a field which he made so strikingly his own.

WILLIAM BLOOM





JOSEPH GOLDBERGER  
1874-1929



## JOSEPH GOLDBERGER, M D

1874-1929

Dr Joseph Goldberger of the United States Public Health Service died at the Naval Hospital, Washington, D C, on Jan 17, 1929, following an illness of several weeks. In his death, his profession has lost one of its ablest scientists, and the loss to the country is irreparable.

Dr Goldberger was born in Austria Hungary on July 16, 1874, and came to the United States with his parents when but a boy. He received his academic education in the public schools of New York and graduated from Bellevue Hospital Medical College. After several years in hospital and private practice, he entered the United States Public Health Service in July, 1899, as an assistant surgeon, he was promoted to the grade of passed assistant surgeon in 1904, and to the grade of surgeon in 1913. His early work included assignments to general medical, quarantine and epidemic diseases. These last mentioned assignments were to epidemics of yellow fever at Tampico, Mexico, Ponce, Porto Rico, Vera Cruz, Mexico, and New Laredo, Texas. At Tampico, he contracted yellow fever during the conduct of his duties. In 1905, he performed highly valued field work during the epidemic of yellow fever in the South.

Dr Goldberger's special qualifications for scientific research were early recognized. He was accordingly attached to the Hygienic Laboratory, Washington, D C, in the fall of 1904, from which institution he conducted his investigations of many public health problems. While he was attached to the laboratory, this work involved prolonged absences and extensive travel, sometimes emergency studies. The latter studies related to dengue fever in south Texas, where he contracted the disease in 1907, to an epidemic of diphtheria in Detroit in 1913, and to straw mite disease in New Jersey, the cause and methods of transmission of which he discovered.

The most notable studies of Dr Goldberger related to measles, typhus fever and pellagra, all of which are major problems, from a public health standpoint. In association with a colleague, he was able to transmit measles to lower animals, throwing light on the period of incubation and infectivity of the disease.

During the winter of 1909-1910, in association with another officer, he studied typhus fever in Mexico City, and contracted a severe attack of the disease. During the winter of 1911-1912, he again carried on studies of typhus fever in Mexico, which were of the greatest importance because they demonstrated the identity of the typhus fever of Mexico and Brill's disease, a mild form of typhus known to prevail in New York and certain other places in the United States for many years.

He also demonstrated that typhus fever is transmitted not only by the body louse, but by the head louse, information of the greatest value in the prevention of this epidemic disease

By far the most important work conducted by Dr Goldberger, however, related to pellagra. This he began in 1913 and vigorously prosecuted until the time of his last illness. In these studies, he was able to utilize his special training and experience in bacteriology, epidemiology and zoology. No scientific worker has been able to approach this problem from as many angles. As a result, he soon became convinced that it was a nutritional disease, due to an unbalanced diet. He set himself the important task of determining, if possible, what features of diet were lacking. The volume of work and the mass of detail have been tremendous. Fortunately, he was able to report advances from time to time. By epidemiologic methods, among children in institutions, he demonstrated conclusively that pellagra is a dietary disease. By extensive feeding experiments, he proved that it is not an infectious disease, and he actually produced the disease in man by a diet which he had concluded was the essential factor of causation. The actual factor necessary for the prevention of the disease he identified, but not in the pure state, and called it pellagra preventive. As a result of his researches, he determined the relative preventive value of this factor in different foods and actually found that by the use of proper diets pellagra could be not only cured but prevented. In connection with this work, he likewise determined that "black tongue" of dogs is a dietary disease closely akin to, if not identical with, pellagra, and he was able to determine symptoms of pellagra in other laboratory animals by feeding, all of which has had a potent influence in stimulating further wide researches in nutrition. Pellagra was first recognized in the United States in 1907. By 1909, it had become a menace to a considerable section of the public. As a result of Dr Goldberger's studies and the prompt utilization of his results by physicians, pellagra is now an entirely preventable disease. Certainly, no more valuable public health research has been conducted in any country within a generation than these studies in pellagra. This disease had existed and been recognized in the old world for 100 years, but almost immediately after its discovery in the new world, it was attacked and the solution for its prevention was determined. In the performance of this great work, Dr Goldberger has erected a lasting monument to himself, the generations to follow will be debtors to the work and achievements of this great man.

Dr Goldberger leaves to his family an illustrious name. He was married to Mary Farrar of New Orleans. They have four children, some of whom have grown to manhood.

R. C. WILLIAMS

# Abstracts from Current Literature

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## Experimental Pathology and Pathologic Physiology

THE EFFECTS OF CARBON ARC RADIATION ON THE BLOOD OF DOGS H S MAYERSON and H LAURENS, *Am J Physiol* **86** 1, 1928

Following a single exposure (abdominal) to carbon arc radiation, there was observed in dogs a temporary increase in plasma volume of from 6 to 37 per cent, with recovery to normal in five hours. Further exposures caused recurrence, but not augmentation, of this dilution, the duration, however, varied with the strength of exposure and the interval between successive exposures. After massive exposures, the initial dilution was followed by a slight concentration. Repeated exposures resulted in a stimulation of the hematopoietic system, indicated by an increase in the red cell count of from 10 to 19 per cent, lasting from three to six weeks. The red cells during the postradiation period were smaller and less saturated with hemoglobin. Blood platelets diminished in number and volume during irradiation, usually with recovery within five hours. Occasionally there was an increase during the postradiation period. A progressive leukopenia, with a marked lowering of the white cell count during the postradiation period, developed during irradiation.

H E EGGERS

THE INFLUENCE OF "HEAT" ON THE SURVIVAL PERIOD OF DOGS AFTER ADRENALECTOMY J M ROGOFF and G N STEWART, *Am J Physiol* **86** 20, 1928

"Heat" in dogs was found to be associated with a marked lengthening of the survival period following suprarenalectomy, and of the period of good health. All survived longer than did any of the more numerous control animals.

H E EGGERS

THE EFFECT OF LIGATION OF THE COMMON BILE DUCT UPON THE APPEARANCE OF TETANY IN THYROPARATHYROIDECTOMIZED DOGS J C BROUGHER, *Am J Physiol* **86** 39, 1928

In dogs, ligation of the common bile duct with or without cholecystectomy, prevents the development of typical parathyroid tetany. This may occur in mild form, in which case its onset is delayed. This delay may be explained in several ways: a lessened excretion of calcium which would otherwise occur in the bile, increased absorption of calcium from the intestine because of the absence of the alkaline bile salts, by which calcium is precipitated, and depression of the central nervous system by the absorbed bile.

H E EGGERS

THE SEASONAL VARIATION IN BASAL METABOLISM F L GUSTAFSON and F G BENEDICT, *Am J Physiol* **86** 43, 1928

Monthly measurements were made of the basal metabolism of twenty young women, with the exception of the months of July, August and September, for a period covering fifteen months. While the determinations varied with stimuli incident to college life, the average values suggested that the rate was at a low level during the winter months, rising during the spring and summer. Many of the results suggested that there is a lowering of metabolic rate during menstruation.

H E EGGERS

NORMAL MENSTRUATION AND GASEOUS METABOLISM F G BENEDICT and M D FINN, *Am J Physiol* **86** 59, 1928

A series of intermittent determinations of basal metabolism made on one woman over a period of twelve years showed an average deviation from the predicted

(Harris-Benedict) heat production of —45 per cent for eighty-nine intermenstrual days, and —75 per cent for thirty-two menstrual days. The lower metabolism during the menstrual period was confirmed by the additional observation that the preponderance of deviations greater than —10 per cent occurred on menstrual days. A similar conclusion was suggested by a series of monthly determinations on twenty college students. Finally, a series of daily observations were made on the first subject, which showed in general that oxygen consumption was lowest and most uniform during the menstrual period, and highest about one week after its cessation.

H E EGGLERS

#### HEMORRHAGIC HYPERGLUCEMIA M G MULINOS, *Am J Physiol* **86** 70, 1928

In cats anesthetized with iso-amyl-ethyl barbituric acid arterial hemorrhage was found to yield blood increasingly rich in reducing substances. That this was not due to the asphyxial outpouring of epinephrine was shown by its occurrence in suprarenalectomized animals. A coincident fall in hemoglobin showed that the hemorrhage had a marked diluting action on the blood, from which the writer deduces that the diluting fluid contains at least as much dextrose as the blood itself.

H E EGGERS

#### THE EFFECT OF VERY EARLY ABLATION OF THE CORPUS LUTEUM UPON EMBRYOS AND UTERUS G W CORNER, *Am J Physiol* **86** 74, 1928

Recently pregnant rabbits, from fourteen to twenty hours after mating, were subjected to complete or partial oophorectomy, with complete or partial removal of the corpora lutea. In the case of complete oophorectomy, there was a failure of the endometrium to develop the changes characteristic of pregnancy, and the blastocytes died soon after entering the uterus. With removal of one ovary and damage to the other, but with survival of one or more corpora lutea, the developments were those of normal pregnancy, after removal of all the corpora lutea, with survival of a portion of ovarian tissue, there was a lack of endometrial development and of that of the ova. The experiments confirm the existence of progestational proliferation of the rabbit's uterus, and support the view that this is dependent on the corpora lutea. They also confirm the view that the corpora lutea are necessary for embryonic implantation, and they suggest that normal implantation is dependent on the progestational proliferation of the endometrium. This same proliferation appears to be necessary to the survival of the free blastocytes during the three or four day interval before the ovum becomes implanted, after its arrival in the uterus.

H E EGGERS

#### CHANGES IN HEMOGLOBIN FOLLOWING REMOVAL OF THE SPLEEN G B RAY, *Am J Physiol* **86** 138, 1928

Determinations were made of the red cell count, total blood pigment and functional hemoglobin in dogs following splenectomy. With the use of the term "nonfunctional pigment" to express the difference between total pigment and hemoglobin, the amount of this present at various times after the operation afforded a physiologic index of the damage following splenectomy. It paralleled neither the red cell count nor the total blood pigment, so that these cannot be regarded as criteria of functional changes in the blood in this condition.

H E EGGERS

#### THE POLYCYTHEMIA OF ACUTE ANOXEMIA AND ITS RELATION TO THE SYMPATHIC-ADRENAL SYSTEM J J IZQUIERDO, *Am J Physiol* **86** 145, 1928

Although brief asphyxia caused by mechanical obstruction causes a prompt polycythemia in normal animals, this effect is probably to be regarded as largely due to the excitement of the animal. If, though, asphyxia is caused by a gradual

lowering of oxygen tension, the element of excitement may be avoided, in cats in these circumstances there may be no excitement, but the animals will react with rapid and shallow respiration, salivation, erection of hair and polycythemia. The last is absent in splenectomized animals. With animals in which the spleen was denervated about one week before the experiment, there may be an anovemic polycythemia greater than that of the normal animal. Since this disappears if the suprarenals are demedullated, it is probably to be ascribed to the extra epinephrine acting on the toneless spleen. Increase of carbon dioxide in the inspired air was without effect in polycythemia.

H E EGGERS

THE EFFECT OF VARIATION IN POSTURE ON THE OUTPUT OF THE HUMAN HEART A GROLLMAN, *Am J Physiol* **86** 285, 1928

Determinations of the circulatory minute volumes of normal men and women in recumbent, sitting and erect postures showed postural variation to be without effect. However, as in the sitting, and even more in the recumbent position there is a decidedly lower vital capacity of the lung, with a lowering of the reserve air by a liter or more, much more time is required in those conditions to bring about thorough gas mixture. The maintenance of constant circulatory rate is explained by three chief factors: the maintenance of tone by the splanchnic area, the increased cardiac action with rise of rate and of blood pressure and the effect of respiratory changes. Fainting in the normal person is explained as occurring in the erect posture with muscular rigidity, so that the imperceptible but constant muscular movements which ordinarily force the blood past the valves of the veins are lacking.

H E EGGERS

THE PENETRATION OF ULTRAVIOLET RAYS INTO LIVE ANIMAL TISSUE W T ANDERSON, JR., and D I MACHT, *Am J Physiol* **86** 320, 1928

The passage of ultraviolet light, of wave lengths of from 2,537 to 3,000 Angstrom units, was studied in the partially detached, but living, skin of the rabbit by means of fluorescent photometry. It was found that there was a transmission of from 6 to 10 per cent through a skin 12 mm thick. With the onset of death of the skin, there was definite reduction in transparency, and dead skin of the same thickness was found to be practically opaque to ultraviolet light shorter than 3,660 Angstrom units.

H E EGGERS

OBSERVATIONS UPON ADRENALECTOMIZED CATS TREATED WITH THE CORTICAL HORMONE F A HARTMAN, F R GRIFFITH, JR., and W E HARTMAN, *Am J Physiol* **86** 360, 1928

In suprarenalectomized cats treated with extracts of suprarenal cortex, a condition was observed simulating that of chronic suprarenal insufficiency. In general, the symptoms were like those of acute insufficiency, but with much more gradual development. In the majority of treated animals, the metabolic rate remained within normal limits for from seven to twenty-nine days after the removal of the second suprarenal. The animals never gained weight and usually lost long before the appearance of terminal symptoms. They were less resistant to cold and to infection, and fatigued more readily than normal animals. Overeating caused a rise of blood urea, and brought on symptoms of suprarenal insufficiency. A darkening of the skin was occasionally observed, and in one cat which survived 300 days there was a chocolate discoloration of the subcutaneous fat. The survival period was not influenced by thyroidectomy and gonadectomy.

H E EGGERS

A COMPARATIVE STUDY OF THE ACID-BASE EQUILIBRIUM OF BILATERALLY NEPHRECTOMIZED AND ADRENALECTOMIZED DOGS W W SWINGLE, *Am J Physiol* **86** 450, 1928

In bilaterally nephrectomized dogs there was no development of acid intoxication. While there was an occasional slight fall in alkali reserve, there was a

striking contrast to the acidosis of suprarenalectomy. A slight increase was found in blood sugar, in contrast to the marked fall observed after suprarenal extirpation. Increase in inorganic phosphates, sulphates and urea was found to follow both nephrectomy and suprarenalectomy. Following nephrectomy, there was a fall of blood chlorides. It is suggested that the acid intoxication of suprarenal insufficiency, and probably of uremia, is of extrarenal origin, since it was not present in nephrectomized dogs with total suppression of renal function.

H E EGGERS

THE ACID INTOXICATION OF ADRENAL INSUFFICIENCY IN DOGS F M YONKMAN, *Am J Physiol* **86** 471, 1928

In suprarenalectomized dogs there was observed a gradual rise of the inorganic phosphorus of the serum, increasing with the symptoms of suprarenal insufficiency. With the first signs of weakness, there is a decline of blood sugar. After this a fluctuation may occur, but there is an invariable terminal drop. The carbon dioxide capacity gradually decreases with the onset of symptoms. The  $p_H$  remains normal until the carbon dioxide capacity falls from 30 to 33 per cent by volume. After this it declines in company with the carbon dioxide capacity, indicating a shift from a compensated acidosis with normal  $p_H$  and low carbon dioxide capacity to an uncompensated condition. The acidosis is due in part to retention of phosphates and sulphates. That there is diminished renal output was indicated by functional tests.

H E EGGERS

ACCUMULATION OF BILE AROUND THE LIVER WAITMAN WALTERS and JESSE L BOILMAN, *J A M A* **91** 239, 1928

The postoperative accumulation of bile around the liver, producing its displacement, is sufficient to cause symptoms of shock and even death if allowed to persist. From our experiments we believe the reaction to be due to interference with the circulation in the inferior vena cava from the downward displacement of the liver. Removal of the forces producing the displacement is followed both clinically and experimentally, by the immediate return of normal circulation and the disappearance of symptoms. Bile accumulating around the liver is rapidly absorbed by the lymphatics of the diaphragm and experimentally is detected in the lymph of a thoracic duct fistula in from two to three minutes after its contact with the peritoneal surface of the diaphragm. This is in contrast to the relatively slow appearance of bile in fluid from such thoracic duct fistulas when there is bile below the liver.

AUTHORS SUMMARY

THE HORMONE TEST FOR PREGNANCY A C SIDDAIL, *J A M A* **91** 779, 1928

The test is based on the effect of the blood serum of pregnant women when injected into white female mice. The positive result consists either in enlargement with increase in weight of the uterus or ovaries of the mice. This test may prove of value in standardizing commercial preparations purporting to contain hormones that act on sex organs. In 142 cases of pregnancy the hormone test proved to have a high degree of accuracy.

THE EFFECT OF INSULIN ON PROTEIN METABOLISM V C KIECH and J M LUCK, *J Biol Chem* **78** 257, 1928

The administration of insulin to the white rat appears to disturb the normal equilibrium between the rate at which its proteins are hydrolyzed and the rate at which the hydrolytic products are in turn degraded to urea.

ARTHUR LOCKE

THE RELATION OF COPPER TO THE HEMOGLOBIN CONTENT OF RAT BLOOD  
J S MCHARGUE, D J HEALY and E S HILL, J Biol Chem **78** 637, 1928

A dietary source of copper is essential to the maintenance of a high hemoglobin level

ARTHUR LOCKE

INFLUENCE OF LIGHT ENVIRONMENT ON THE GROWTH AND NUTRITION OF  
NORMAL RABBITS WITH ESPECIAL REFERENCE TO THE ACTION OF NEON  
LIGHT WADE H BROWN, J Exper Med **48** 31 and 57, 1928

The influence of light environment on the growth and nutrition of normal rabbits was studied by comparing the weight curves of animals living under different environmental conditions for periods of from four to eight months and the effects of change from one environment to another. Prolonged exposure to neon light was compared with confinement in the dark and exposure to diffuse, filtered sunlight of varying intensity. The results of the experiments showed that growth and nutrition were greatly affected by the light environment in which the animals lived. The effects produced by a given environment varied with the color or breed of the animal and appeared to be out of proportion to the differences in the intensity of the light or the energy represented. In a series of experiments dealing with the influence of light environment on normal rabbits the growth of hair over shaved areas was used as an index of functional activity. The conditions compared were exposure to neon light, complete exclusion of light and exposure to diffuse, filtered sunlight of varying intensity. It was found that prolonged existence under these conditions affected the proliferative activity of hair follicles in a manner and to an extent comparable with the effects produced by the same environmental conditions on the growth and nutrition of the animals themselves.

AUTHOR'S SUMMARY

THE EFFECT OF METHYLENE BLUE AND OTHER DYES UPON THE OXYGEN  
CONSUMPTION OF MAMMALIAN AND AVIAN ERYTHROCYTES GEORGE A  
HARROP, JR., and E S GUZMAN BARRON, J Exper Med **48** 207, 1928

The respiratory metabolism of non-nucleated mammalian erythrocytes is enormously accelerated and approaches the magnitude of the metabolism of the nucleated erythrocytes of birds on the addition of methylene blue (and certain other dyes), to a final concentration of from 0.005 to 0.0005 per cent. In the presence of methylene blue, the respiration is accelerated even when thousandth molar KCN is also present. The accelerated respiration due to methylene blue occurs at room temperature but it is most active at 38 C. Methylene blue in the foregoing concentration accelerates the respiration of avian (goose) erythrocytes to a much smaller extent than it does the respiration of the erythrocytes of mammalian blood, while the effect on anemic goose blood seems to be less than it is on cells of normal goose blood. Owing to a rather large initial carbon dioxide formation in defibrinated blood on incubation, which may not be related to the immediate respiratory process, proper respiratory quotients cannot be obtained in whole blood. When the cells are separated from the serum and suspended in Locke's solution, respiratory quotients are obtained on incubation comparable to those of other resting mammalian cells, as well as of the actively respiring erythrocytes of birds. The hypothesis is advanced that methylene blue acts in the role of an oxygen carrier, supplying a substance which has disappeared from adult mammalian non-nucleated erythrocytes and restoring their metabolic activity to an extent comparable to that of the young immature forms or to that of the actively respiring avian (goose) blood.

AUTHORS' SUMMARY

EXPERIMENTAL STUDY OF DIATHERMY RONALD V CHRISTIE, J Exper Med  
**48** 235, 1928

A method is described for measuring the relative impedance of living cells to diathermy currents. The diathermy current penetrates the living cell, and heat

production is intracellular as well as extracellular. A small proportion of the impedance of living cells to the diathermy current seems not to lead to the production of heat. Evidence is given that the addition of saponin produces an appreciable increase in the conductivity of an electrolyte. Its use is therefore contraindicated when electrical measurements are being made on biologic material. The currents used in diathermy behave as do high frequency currents of the pure sine wave form in respect to their passage through biologic material.

#### AUTHOR'S SUMMARY

#### EFFECTS OF SPERM INJECTIONS INTO FEMALE RABBITS W. T. POMMERENKE, *Physiol Zool* **1** 97, 1928

Rabbits were given intravenous, intraperitoneal and intravaginal injections of rabbit spermatozoa and extracts of the testis. Others were given injections of rat spermatozoa. The serums and vaginal secretions of female rabbits which have received repeated intravenous or intraperitoneal injections of rabbit spermatozoa become highly toxic for rabbit spermatozoa. The life of spermatozoa normally deposited in the female genital tract of the rabbit is noticeably shortened by such previous injections of rabbit spermatozoa. Similar results were obtained when Ringer's solution extracts of fresh rabbit testes were repeatedly injected. There was no apparent effect on the estrous cycle, but injections given during pregnancy sometimes resulted in abortion or resorption of the fetuses.

Repeated injection of rabbit spermatozoa or of fresh testicular extracts into female rabbits may be followed by infertility lasting for from four to twenty-five weeks, and on return of fertility the number of young born in the first litters tend to be smaller than the earlier litter average. Control rabbits given corresponding injections of extracts of rabbit salivary glands and the ejaculated material coming from vasectomized male rabbits showed none of the foregoing results. Spermatoxins developed by means of rabbit spermatozoa are also toxic for rat spermatozoa, and vice versa. Repeated intravaginal injection of rabbit spermatozoa may induce antigenic effects in the blood and vaginal secretions of the experimental animals, but evidence of sterility is inconclusive.

#### THE TEMPERATURE OF NORMAL RABBITS P. LAZARUS-BARLOW, *J Pathol & Bact* **31** 517, 1928

Except for a sudden increase in temperature after a cool period, or for a close thundery atmosphere, the temperature of a normal rabbit varies little with the external temperature. The temperature varies within rather wide limits and is subject to sudden rises for no apparent reason. Food causes a rise in temperature. A rise or fall from the mean of 2 F is apparently significant. Sudden rises above 104 F cannot be considered pathologic unless sustained.

#### THE CIRCULATION RATE IN SOME PATHOLOGICAL STATES, WITH OBSERVATIONS ON THE EFFECT OF DIGITALIS J. G. KINMONTH, *Quart J Med* **21** 277, 1928

One hundred and sixty-three determinations of the circulation rate have been made by the ethyl iodide method on twenty-four patients suffering from various cardiac lesions, from anemia, from myxedema and from exophthalmic goiter. Aortic incompetence and early mitral stenosis do not directly affect the circulation rate. In a case of pulsus bigeminus resulting from digitalis, the bigeminal rhythm did not affect the cardiac output. In complete heart block, the output at each beat is large. In cardiac failure the circulation rate is low, this being due in ordinary types to a failure of the myocardium to maintain a sufficient output per beat with, in cases of auricular fibrillation, rapid irregular tachycardia a possible contributory factor. The circulation rate may be increased, decreased or unaffected by digitalis, different effects occurring in different patients and in the same patient at different times. An increase appears most likely to occur when



there are signs of cardiac insufficiency and a low circulation rate, but in such cases does not invariably occur. When signs of failure are absent or little marked and the circulation rate is not definitely low, an increase is less likely, the circulation rate usually remaining unaltered or decreasing. In cases of anemia, definite changes in circulation rate were not discovered. In exophthalmic goiter, the circulation rate tends to be high and in myxedema low. N ENZER

AN INSULIN-RESISTANT DIABETIC R D LAWRENCE Quart J Med **21** 359, 1928

An unusual resistance to insulin was present in a young diabetic patient. In 1925 the patient's glycosuria was controlled by 40 units of insulin. A year later 100 units was necessary to maintain a normal blood sugar level, and six months later, on 220 units of insulin he excreted from 5 to 10 Gm of sugar on a diet of carbohydrate, 60, protein, 80, and fat, 150. When insulin was omitted, coma supervened. The usual conditions encountered in diabetic patients resistant to insulin were absent in this case in which the blood sugar rose to extremely high levels after the injection of carbohydrate in spite of large doses of insulin. That this was not due to delayed insulin action or absorption was shown by the reduction of the blood sugar at a normal rate in the fasting condition. It would seem that there was a failure here of insulin to split up the injected carbohydrate. This failure to convert and store carbohydrate was shown by the spontaneous fall in the blood sugar when the patient was starved. Apparently, the insulin was able to control only the neoglucogenesis and ketogenesis from protein and fats. Possibly an enzyme other than insulin was lacking. N ENZER

CREATINE AND RIGIDITY M HIRST and E G IMRIE, Quart J Med **21** 401, 1928

In parkinsonian rigidity, creatinuria occurs regularly. The amount of creatine excreted expressed as a fraction of the body weight seems to bear a direct relationship to the degree of rigidity. N ENZER

CARBOHYDRATE AND FAT METABOLISM OF THE TISSUES HANS-JOACHIM ARNDT, Beitr z path Anat u z allg Path **79** 523, 1928

By removal of small pieces of liver, muscle and other tissue at various times in the experiment, Arndt was able to trace changes in glycogen under conditions of fasting and the administration of insulin. Fasting was seen to cause glycogen to disappear from the liver in from one-half day to two days but was rapidly returned on large doses of sugar. While the fat of the body was practically free of glycogen, an overfeeding with sugar could cause comparatively large quantities of glycogen to appear in the fat cells of the fatty tissue. Though most of this disappeared when the animal was put back on a regular diet, the glycogen appeared to have been synthesized independently of the liver. The fat itself was not influenced by any of the foregoing substances or by the injection of insulin. Insulin, however, may cause a marked decrease in hypercholesteremia. The glycogen of the liver was greatly reduced when insulin was given in large and moderate sized doses but was increased when given in small doses with sugar. Insulin had been found to act through the placenta. It could act on the fetus whose blood sugar ran parallel with the mother's and the level was dependent on the doses of insulin. The depancreatized pregnant dog did not become hyperglycemic or show glycosuria. It seems that the fetal pancreas can secrete for the mother. There was no evidence in favor of the passage of insulin through the mammary gland. In rabbits, it was noted that continuous small doses of insulin had an intensifying action on the blood sugar and some animals progressed to a hypoglycemia. This was not noted in man. Insulin in man seemed to cause a glycogen formation in diabetes. When large doses of insulin and sugar were given, patients who had died of diabetic coma showed glycogen in the capillaries.

and within blood vessels but not in the liver cells, but those diabetic patients who had died of intercurrent disease showed the usual glycogen in the liver

JESSE LOUIS SERBY

FAT METABOLISM FOLLOWING SPLENECTOMY S LLITES, *Klin Wchnschr* 7 1186, 1928

After splenectomy, the splitting of the neutral fat by the liver is disturbed. Vicariously, the neutral fats are partially split in the lungs, and the oxidation of the lower fatty acids is delayed and disturbed (acetonemia)

E F HIRSCH

THE PHARMACOLOGY AND PHYSIOLOGY OF IRON E STARKENSTLIN and H WEDEN, *Klin Wchnschr* 7 1220, 1928

The rapidity and completeness with which iron is deposited in the liver and spleen is an index of its pharmacologic, and probably also therapeutic, uselessness, as well as of its biologic function in the organism. Active iron circulates for a long time in the organism and is brought by the blood to all tissues, except the spleen.

The spleen absorbs primarily only the inactive ferric compounds, which are gradually liberated again. In the liver the iron is deposited only when it is reduced to an inactive form which probably is used in the building up of hemoglobin, but not for the biologic catalytic and pharmacologic iron activities in the organism.

E F HIRSCH

THE RELATIONS BETWEEN THE PAROTID, THE PANCREAS, THE SUGAR OF THE BLOOD AND DIABETES MELLITUS S SFILIC, *Klin Wchnschr* 7 1228, 1928

Ligation of the parotid duct was carried out in dogs to determine whether the effect of an internal secretion could be demonstrated. By this procedure the sugar concentration of the blood is maintained at a persistently low level. Dogs with pancreatic diabetes are not benefited by ligation of the parotid duct. If the duct is ligated before extirpation of the pancreas, the hyperglycemia is apparently not severe and the emaciation not so progressive. On the basis of results obtained in dogs, the parotid ducts of ten patients with diabetes mellitus were ligated. Of these, seven seemed to be influenced favorably and three apparently not.

AUTHORS SUMMARY

DYE ADSORPTION BY THE SERUM OF PERSONS WITH LEAD POISONING A SEITZ, *Klin Wchnschr* 7 1234, 1928

The adsorption power for dyes (naphthol yellow) of the serum of many patients with lead poisoning is diminished. In the absence of organic diseases, the results of such an adsorption test may be of value.

AUTHOR'S SUMMARY

THE DIAGNOSIS OF PREGNANCY BY DEMONSTRATION IN THE URINE OF THE HORMONE OF THE ANTERIOR LOBE OF THE HYPOPHYSIS S ASCHHOFIM and B ZONDEK, *Klin Wchnschr* 7 1404 and 1453, 1928

The hormones of the ovary and of the anterior lobe of the hypophysis, produced in excess during pregnancy, are excreted in large quantities in the urine. The demonstration of ovarian hormone in the urine is not suitable as a biologic diagnostic test for pregnancy, because with functional disturbances of the ovary (climacteric, hyperhormone amenorrhea) large amounts of the hormone are excreted in the urine. The demonstration of the hormone of the anterior lobe of the hypophysis in small amounts of urine (from 12 to 24 cc) according to a prescribed method is an excellent method for diagnosing pregnancy during the first months. The urine from 258 female (nonpregnant) and male patients was

tested for the presence of the hormone of the anterior lobe of the hypophysis. The hormone was found in four of these, an error in the diagnosis of pregnancy of 16 per cent. The urine of 197 pregnant women was tested in a similar way and of these 4, or 2 per cent, had no hormone content.

E F HIRSCH

#### METABOLISM WITH CARDIAC DISEASE D LASZLO, *Klin Wchnschr* 7 1411, 1928

There is a specific diminution of the phosphoric acid of the blood in uncompensated heart disease. During the period of improvement the phosphoric acid is retained, and the phosphoric acid added to the diet is also retained. The heart muscle and especially the skeletal muscle in those dying from heart disease have a diminished phosphoric acid content. The excretion of creatinine and uric acid is increased. In spite of the normal nonprotein nitrogen content of the blood with heart disease, creatinine and uric acid are increased. With muscular activity (work) in cardiac decompensation there is a marked increase of the lactic acid, uric acid and creatinine of the blood, while the inorganic phosphoric acid diminishes.

AUTHOR'S CONCLUSION

#### THE ACTIVATION OF INSULIN IN ADULTS WITHOUT DIABETES E VOGT, *Klin Wchnschr* 7 1460, 1928

Maximum activation of insulin is obtained by adding the serum of women obtained immediately before the onset of menstruation. Protein-free hormone of the follicles acts in the same way. In contrast, the serum of women after operative or roentgen-ray castration has little activating property. Activation occurs also by exposure to sunlight or to a carcinoma dose of roentgen-ray.

AUTHOR'S SUMMARY

#### CHANGES IN THE K, CA AND CHOLIN CONTENT OF THE BLOOD IN ANGINA PECTORIS D DANIELOPOLU and M MAXIM, *Klin Wchnschr* 7 1466, 1928

There is a marked increase of the potassium and cholin during the anginal attack. These rapidly decrease within half an hour. Toward the end of the anginal attack, there is a slight increase of the calcium. Similar changes were observed in dogs with stimulation of the sinus caroticus.

AUTHORS' SUMMARY

#### THE STOMACH AS A COREGULATOR OF THE ACID-BASE EQUILIBRIUM M BAKALTSCHUK, *Klin Wchnschr* 7 1551, 1928

The increased acidity of the gastric secretion with inhalation of 3 and 5 per cent carbon dioxide should be regarded as a compensatory process caused by the acidosis. The stomach is important in regulating the acid-base equilibrium. The place where the stomach enters as regulator of the acid-base equilibrium is determined by the sufficiency of the important regulators, on the one hand, and the buffer capacity of the organism, on the other.

AUTHOR'S SUMMARY

#### THE HYPOPHYSIS AND HYPOTHALAMUS IN EXPERIMENTAL DIABETES INSIPIDUS P TRENDLENBURG, *Klin Wchnschr* 7 1679, 1928

After removal of the hypophysis, considerable amounts appear in the tuber cinereum of a substance which acts on the excretion of urine like the posterior lobe of the hypophysis and which is present only in traces in the tuber cinereum of normal animals. Diabetes insipidus may be hormonal in character, and when the production in the posterior lobe of a substance which inhibits urinary secretion ceases, then vicariously the tuber cinereum becomes active. Only after the destruction of this function is an irreparable diabetes insipidus established.

AUTHOR'S SUMMARY

LACTIC ACID OF THE BLOOD IN DISEASE OF THE LIVER H. SCHUMACHER,  
 Klin Wchnsch 7 1733, 1928

In severe forms of injury of the liver, the lactic acid content of the blood is increased, although in mild disease of the liver this may not be true. After intravenous injection of sodium lactate equivalent to 4 Gm. of lactic acid in 20 cc. of water, the lactic acid content of the blood in disease of the liver remains increased for a longer time than when the liver functions normally. Exceptions to this are observed in certain healthy persons.

E. F. HIRSCH

ADMINISTRATION OF INSULIN THROUGH THE PORTAL SYSTEM IN DOGS DAVID  
 H. BOGGIJD, Acta path et microbiol Scandinav 5 118, 1928

The experiments indicate that in dogs with a normal, or only slightly elevated, blood sugar level insulin has the same quantitative effect on the blood sugar when it is carried directly to the liver by way of the portal system as it has when introduced through the somatic peripheral circulation. Probably, however, parallel experiments should be made on dogs with hyperglycemia caused by pronounced diabetes, or from administration of dextrose, because experiments by Lewis and Magenta indicate that low blood sugar values after injection of insulin result in increased secretion of epinephrine.

AUTHORS SUMMARY

### Pathologic Anatomy

COARCTATION OF THE AORTA OF THE ADULT TYPE W. F. HAMILTON and  
 M. E. ABBOTT, Am Heart J 3 381 and 574, 1928

In the adult type of aortic coarctation a pathologic condition exists without counterpart in normal intra-uterine life. It consists of a sharp constriction amounting, in some cases, to a complete obliteration of the lumen of the descending aorta, adjacent to the insertion of the ductus arteriosus. At times, the constriction is so sudden and deep that the descending arch appears as if a ligature had been tied around it, and above and below this the aorta bulges outward in hour-glass fashion. Internally, the effect of the external strangulation in narrowing the lumen of the vessel is accentuated frequently by a fold or septum which stretches across that which remains of the aortic lumen, partially or completely closing it. The great vessels of the arch, especially the innominate and left subclavian arteries, are usually dilated, as are also the first three intercostals emerging below the stricture and the deep epigastric arteries, for it is by means of these vessels that the collateral circulation maintains life. Although the cause of coarctation is obscure, traction by the ligamentum arteriosum increases the kinking of the descending arch and at times produces a tent-shaped aneurysm of the aorta with its apex toward the ligamentum. Loriga believes the condition begins in the primitive left aorta, which unites the left fourth (aortic) arch with the fifth and sixth arches of this side.

A reproduction of a table illustrates the sex and age incidence in 200 cases.

Age in Decades	Males	Females	Sex Unknown	Totals
3 to 10 years	6	3		9
10 to 20 years	34	11		45
20 to 30 years	34	13	2	49
30 to 40 years	34	8	3	45
40 to 50 years	21	7		28
50 to 60 years	9	3		12
60 to 70 years	7	3		10
70 to 92 years	2			2
	147	48	5	200

The degree of stenosis was moderate in 45 bodies, and the aperture allowed the passage of the little finger, extreme in 108, and admitted objects from a bristle to 6 mm in diameter, and complete in the remaining 47. Minor cardiac anomalies were present frequently in the form of bicuspid aortic valves, anomalous origins of the arteries from the arch, persistent superior vena cava of the left side and defects of the interauricular and interventricular septums. In the body at large, there were additional anomalies, as hypospadias, absence of the left kidney, ureter and seminal vesicle, diaphragmatic hernia and subluxation of the joints. The causes of death were spontaneous rupture of the heart and ascending aorta in 35 cases, rupture at the coarctation in 5, aneurysm, saccular or dissecting, in 39, mycotic endocarditis in 14, 4 of which were due to *Streptococcus viridans*, cerebral lesions in 26, of which 1 was due to embolism, the rest to hemorrhage, decompensation in 60, sudden heart failure in 17 and other causes in 36. The case report presented concerns a boy, aged 14, who for four years had had dyspnea, precordial pain, weakness and cyanotic clubbed fingers. The radial pulse was typically collapsing while the femoral and tibial pulsations were impalpable. There was a rough systolic heart murmur, with a blood pressure of 150 systolic and 50 diastolic. Death followed a hemiplegia, which rendered the right arm and leg powerless. Autopsy was confined to the trunk. There was a coarctation of the aorta at the site of the ligamentum arteriosum, and the vessel wall on either side of this presented a smooth, shining biconcave surface suggesting an anomalous development from the primitive aortic arch at its junction with the left sixth arch. In addition, there were a bicuspid aortic valve, subaortic stenosis and an anomalous vessel from the descending arch.

GEORGE RUKSTINAT

#### TISSUE CHANGES IN PARATHYROID TETANY AND IN GUANIDINE POISONING

L. A. ELKOURIE and E. LARSON, *Am J Physiol* **87** 124, 1928

When the changes induced by parathyroid tetany and those induced by guanidine intoxication in dogs were compared, the two conditions were found to have very different clinical syndromes, the visceral congestion of parathyroid tetany was lacking in guanidine poisoning, and the hepatic fatty degeneration of the latter was absent in the former. Necrosis of the liver was present in both.

H. E. EGERS

#### NECROPSY FINDINGS UNDER CRACKED-POT TYMPANY. JOSEPH WALSH, *Am Rev Tuberc* **18** 202, 1928

From a necropsy study of eleven cases it would appear that, when cracked-pot tympany occurs in tuberculosis of the lungs apart from pleural effusion, the diagnosis of superimposed cavities was practically assured. The single exception found in these cases was associated with a rare condition in which a combination of cavity and central consolidations existed, so that a blending of superimposed tympany was produced.

H. J. CORPER

#### THE RELATIVE INCIDENCE OF CALCIFIED LESIONS IN THE TRACHEOBRONCHIAL, CERVICAL AND ABDOMINAL LYMPH NODLS. F. H. FRASER, *Am Rev Tuberc* **18** 336, 1928

Roentgen examination was made of 151 children, including 31 with tracheo-bronchial lesions, in order to determine whether there were calcified lymph nodes in the neck and abdomen. Two cases with cervical calcium were found. Four had cervical tuberculosis without demonstrable calcium. Abdominal calcified nodes were present in two cases without signs or symptoms. All roentgenographically positive patients reacted positively to tuberculin and were without pulmonary lesions.

H. J. CORPER

THE INCIDENCE OF ROENTGNOGRAPHICALLY OBSERVED CALCIFIED PULMONARY FOCI AND THEIR SIGNIFICANCE JOHN F FARRELL, JR, *Am Rev Tuberc* 18 344, 1928

Of 1,034 adult patients whose chests were examined by the roentgen ray, 801, or 77.46 per cent, presented evidence of a primary "Affekt" or of a calcified reinfection. Of this group, 750, or 72.93 per cent, presented primary "Affekt." The lower portion of the right lung, the best aerated portion, exhibited the highest incidence of calcified foci. There was a slightly higher incidence of primary foci of the lung in the male patients. In those without roentgen evidence of apical tuberculosis of the adult type, there was a higher incidence of calcification than in those with clinical tuberculosis. No relationship as to age was established in this group of patients, whose ages ranged from 15 to 84 years. With advancing age, there was an increase in the proportion of patients who showed the more extensive degrees of calcification.

H J CORPER

THE DISTRIBUTION OF VALVES AND THE FIRST APPEARANCE OF LYMPHATIC DIRECTION IN THE DRAINAGE OF LYMPH IN THE HUMAN LUNG OTTO F KAMPMEIER, *Am Rev Tuberc* 18 360, 1928

Lymph vessels begin to invade the lung in human fetuses of 2 months. At the end of the third month, not only have they traversed the entire organ by extending along the bronchi, pulmonary arteries and veins, but they are creating a subpleural network. Developing valves, already present in the lymphatics of the jugulosubclavian territory at the end of the second month of prenatal life, arise in the lymphatic plexus of the mediastinum shortly afterward, and in that of the hilum of the lung not more than a month later. Despite the fact that the lung does not perform its functions until birth, it in no wise lags behind any other part of the body in the prompt construction of its lymphatic organization. Its valves become exceedingly numerous in the period from the third to the fourth months. The mode of valvulogenesis in the pulmonary lymphatics conforms to that in the peripheral lymphatic plexuses elsewhere in the body. A valve originates either by the tangential ingrowth of one lymph vessel into another during the formation of the plexus, or from intimal flanges proliferated at the mouth of confluences established earlier. The valves of the deep lymphatics in the hilum of the lung point toward the mediastinum, and consequently send the lymph stream in that direction. In the channels connecting the deep pulmonary lymphatics and the peripheral or subpleural plexus, most valves point outward, that is, toward the pleura, however, a few instances occur, especially at the margins of the lobes, in which they are turned in the reverse direction. In the material examined for the arrangement of the lymphatic valves in the lung (in fetuses from the middle of intra-uterine life, and in a new-born infant who had breathed), these structures were found in great numbers in the subpleural plexus on the medial face of the lung next to the heart, in moderate abundance on the diaphragmatic surface and on the costal surface near its ventral border, but were absent on the dorsal side and at the apex. This distribution represents a striking demonstration of the purpose of the valves as regulators of the lymph drainage when it tends to be disturbed or impeded by a compressive force on it externally, as by muscular action. It was further observed that the channels of the lymphatic plexus which bore numerous valves, particularly those on the medial or cardiac side of the lung, are larger and more voluminous than the valveless ones on the dorsal side. The distinctions described in the lymphatic volume and valvular distribution, signifying differences in the underlying hydrostatic conditions, suggest a possible relationship with the diversity in the course of the tuberculous process, for example, in the different parts of the lung.

H J CORPER

MILIARY TUBERCULOSIS IN CHILDHOOD JOSEPH GREENGARD, *Am Rev Tuberc* 18 392, 1928

Fifty-four cases of miliary tuberculosis in childhood are reviewed clinically, and complete observations at autopsy are discussed in thirty-five of these. Tuberc-

culous meningitis occurred in 80 per cent of the cases in which autopsy had been performed. Caseation of the tracheobronchial lymph nodes was universally present in the series in which autopsies were performed. Caseous lesions within the lung tissue, which appeared to represent the primary nidus of infection, were noted in twenty-four cases, and pulmonary cavitation was seen in five. Caseation of mesenteric lymph nodes was present in twenty-four cases, and was unaccompanied by advanced tuberculosis of the gastro-intestinal tract in most instances. The occurrence of suppurative otitis media as a concomitant lesion in these cases was noted.

H J CORPER

INCIDENCE OF PLEURAL LESIONS AS SHOWN BY ROENTGENOGRAPHS IN CHILDREN KNOWN TO BE TUBERCULOUS LLOYD B DICKEY and L H GARLAND, *Am Rev Tuberc* **18** 404, 1928

In a series of roentgenograms of the chests of 327 children known to be tuberculous, and in a control series of 50, a surprisingly high incidence of pleural lesions can be demonstrated. A high incidence is shown in the larger positive series for the 1 to 2 year age group, the age at which the evidence of tuberculous pleurisy, at least, is considered to be rare. Fifty-eight per cent of patients examined at this age showed pleural lesions roentgenologically. No relation could be shown between pleural lesions and the enlargement of hilum lymph nodes. Pleural lesions in children who reacted positively to tuberculin tests were no more common than in those who reacted negatively.

H J CORPER

BRONCHOLITHIASIS BARNET P STIVELMAN, *Am Rev Tuberc* **18** 430, 1928

A patient is reported who engaged in an occupation which was the direct cause of his silicotic process of the lungs. As is a common occurrence in such cases, this patient developed phthisis. No light was shed on the etiology of the multiple lung-stone formation, although it is possible that the irritating silica-dust particles, in addition to calling forth their distinctive reaction, also formed the nuclei of future calculi. Definite bronchial colic accompanied the expulsion of the lung-stones, and it is fair to assume that one of these attacks of forced expiratory dyspnea was the cause of the rupture of the lung of the left side at a point already weakened by a tuberculous process or a subpleural emphysematous bleb.

H J CORPER

CHANGES IN THE BRAIN IN INCREASED INTRACRANIAL PRESSURE GEORGE B HASSIN, *Arch Neurol & Psychiat* **20** 1172, 1928

Increased intracranial pressure produces typical histologic changes in the brain. The changes are degenerative, associated with reactive glia phenomena and are analogous to the changes that result from prolonged pressure (by a tumor) on the brain or spinal cord. In the corpus callosum, optic nerve, chiasm and optic tract, the changes are diffuse and noticeable. In the ganglion cells, they are mild. The degenerative changes are combined with areas of rarefaction which are due to stasis of tissue fluids and accumulation, in some instances, of catabolic products, such as basophil-metachromatic substances, lipoids and methyl blue granules. The extent of the changes varies according to the intensity and the duration of the increased pressure. The histologic changes in pressure are of mechanical origin and are due, as in the corpus callosum, to the actual tearing of nerve fibers or to nutritional disturbances brought on in some parts of the brain by stasis of the tissue fluids. The subarachnoid space and the blood vessels usually exhibit proliferative reactive phenomena. When due to tumors, the changes produced by increased intracranial pressure are more marked in extracranial than in intracerebral types of tumor.

AUTHOR'S SUMMARY

PROGRESSIVE DEGENERATIVE SUBCORTICAL ENCEPHALOPATHY (SCHILDER'S DISEASE) JOSEPH H GLOBUS and ISRAEL STRAUSS, Arch Neurol & Psychiat **20** 1190, 1928

Progressive degenerative subcortical encephalopathy is the name suggested for a demyelinating and sclerosing process in the brain of young children involving the white matter without involvement of the gray matter of the cerebral and cerebellar hemispheres. The disease may be due to some toxic factor, of unknown nature, which affects the normal growth of the parenchymatous structures in the subcortical regions of the brain, causes their dissolution and results in proliferative glial changes. Clinically, it is characterized by a rather abrupt onset of illness, which often takes the character of a gastro-intestinal disturbance, and which, after a short period of apparent recovery, is followed by a series of generalized cerebral manifestations. Among the latter, mental disorientation, spastic paralysis accompanied by advancing rigidity, contractures and convulsive seizures appear in varying sequence. Advancing blindness with or without optic atrophy, deafness and aphasia may develop at any stage of the illness, though most frequently early in the clinical course. Some of the conditions described as chronic encephalomyelomalacia, diffuse sclerosis, perivascular myelin necrosis, encephalitis periaxialis diffusa, sclerosing encephaloleukopathia and interlobar symmetrical sclerosis should be grouped under the general name of progressive degenerative subcortical encephalopathy.

#### AUTHORS' SUMMARY

THE BRAIN IN MONGOLIAN IDIOCY LEO M DAVIDOFF, Arch Neurol & Psychiat **20** 1229 1928

The brain in mongolian idiocy shows agenesis, as evidenced by cell poverty and failure of gyral development (there probably is also a degenerative process in very early life, increasing the paucity of the ganglion cells in the cerebral cortex), aplasia, as shown by its small size in comparison with that of children of corresponding age and paragenesis, as demonstrated by the frequent occurrence of anomalies.

#### AUTHOR'S SUMMARY

PERSISTENT THYMUS IN EXOPHTHALMIC GOITER E B POTTER, CONTRIBUTIONS TO MEDICAL SCIENCE DEDICATED TO A S WARTHIN, Ann Arbor, George Wahr, 1927, pp 205-220

Among the records of 2,300 autopsies in the pathologic laboratory of the University of Michigan, Potter found twenty-two proved cases of exophthalmic goiter. In nineteen cases, death was said to be due to thyrotoxicosis, in the remaining three cases pneumonia was the stated cause of death. Hyperplasia of the thymus, as well as generalized lymphoid hyperplasia, was found in every case. These individuals belong to a distinct diathesis, the so-called "Graves' constitution (Warthin)."

#### WALTER M SIMPSON

SIGNIFICANCE OF KIDNEY INFILTRATIONS IN THE GROSS PATHOLOGICAL DIAGNOSIS OF LYMPHOBLASTOMA C H FORTUNE, CONTRIBUTIONS TO MEDICAL SCIENCE DEDICATED TO A S WARTHIN, Ann Arbor, George Wahr, 1927, pp 221-231

Fortune lays emphasis on the value of grossly visible lymphoblastomatous infiltrations of the kidney in differentiating lymphoblastoma from Hodgkin's disease, generalized lymphoid hyperplasia due to infection or metastatic carcinoma. Lymphoblastomatous infiltrations of the liver occur with almost equal frequency, but the renal changes are more easily recognized on gross inspection. Most characteristic is the focal type, in which the lesions are usually cortical and are seen as circumscribed, whitish, firm areas when the fibrous capsule is stripped back. In some cases, the infiltrations are more diffuse, resembling the "large white kidney" of



nephritis On section, there are often found pale, firm streaks in the labyrinthine areas, running radially and more or less clearly differentiated from the surrounding kidney substance

WALTER M SIMPSON

ABERRANT PANCREATIC TISSUE, AN ANALYSIS OF 150 HUMAN CASES WITH A NEW CASE WALTER M SIMPSON, CONTRIBUTIONS TO MEDICAL SCIENCE DEDICATED TO A S WARTHIN, Ann Arbor, George Wahr, 1927, pp 435-459

Simpson reviews the world's literature concerned with aberrant pancreatic tissue, and summarizes 150 cases in tabular form An additional case of pancreas accessorium associated with aberrant Brunner's glands in the stomach wall, mistaken clinically for carcinoma, is recorded The mucosa overlying the pancreatic tissue was intact and showed a distinct central funnel-like umbilication, lined by typical duodenal mucosa, toward which the large excretory ducts converged The pancreatic lobules were most abundant in the subserosa, while the ducts were found in large numbers in the muscularis, simulating the microscopic picture of adenomyoma or infiltrating adenocarcinoma Many islands of Langerhans were found lying free in the muscularis, widely separated from the pancreatic acini In the ducts was a finely granular albuminoid precipitate, similar to that seen in the pancreatic ducts proper, giving probable evidence of functional activity The developmental genesis of these misplaced nodules is discussed in detail, together with a discussion of the frequent association of accessory pancreatic tissue with diverticula of the stomach, duodenum, jejunum or ileum Emphasis is placed on the growing interest in aberrant pancreatic tissue because of the frequency with which they are mistaken, clinically and roentgenologically, for neoplastic growths

AUTHOR'S ABSTRACT

EXPERIMENTAL EDEMA AS AN AID TO HISTOPATHOLOGIC STUDIES S R HAYTHORN, CONTRIBUTIONS TO MEDICAL SCIENCE DEDICATED TO A S WARTHIN, Ann Arbor, George Wahr, 1927, pp 491-501

Edema, when produced artificially in connection with specific experimental lesions, may serve as an aid in studying the cells taking part in the reactions under investigation Its mode of action is that of flushing the tissues with fluid and relieving the pressure of surrounding elements so that the cells become separated and may then be subjected to individual examination It is especially useful when used together with special technical methods designed to bring out cell characteristics

Haythorn found the procedure useful in studies on anthracosis, the identification of pigment phagocytes, the histogenesis of the tubercle and on the origin of the Langerhans giant cell The author is of the opinion that the method probably possesses a wide field of application

WALTER M SIMPSON

INVASION OF THE SKULL BY DURAL TUMORS J TAYLOR, Brit J Surg **16** 6, 1928

One may regard the dural tumors as growths of slow spread, local malignancy and occasional metastasis Their powers of malignant infiltration are seen in their invasion of the coverings of the brain, but only in rare instances do they cross the arachnoid spaces to penetrate the brain itself This last character of failure to cross the arachnoid they share with growths arising in the brain, which do not commonly invade the dura They are exactly paralleled in both their main varieties by the periosteal sarcomas of the long bones, the difference between the dural and periosteal growths being found in the degree rather than in the fact of malignancy in the latter The observations given in this communication certainly in no way indicate the arachnoid as the source of origin of these tumors, nor, it should be pointed out, do they deny such a possibility, because it

has been shown that malignant growths of divers characters may result in identical bony changes, provided they invade the appropriate layers of the bone and periosteum. These observations, however, undoubtedly show that the normal proliferation of the arachnoid into the substance of the dura has no special and unique influence on the form of the growth. They further suggest that the form and spread of the tumors are related to the function of the dura as a periosteum rather than as a covering for the brain. In the presence of the exhaustive labors that have been devoted toward the determination of the tissues from which the dural tumors arise, the writer does not feel qualified to express his opinion on this subject. He rather wishes to emphasize that the facts of their form and growth are those here described, that if these are critically examined, the dural tumors, whatever their origin, take their place naturally among the more commonplace pathologic processes. Thus the attribution to them of characters special and unique is warranted neither by clinical nor by pathologic facts.

## AUTHOR'S SUMMARY

URETHRAL DIVERTICULA T. B. MOUAT, *Brit J Surg* 16 51, 1928

Urethral diverticula may be congenital or acquired, and the causes of the acquired variety vary in the different portions of the canal. In the prostatic urethra, pouches of this kind are most commonly acquired from the gradual increase in size, and communication with the urethra, of a sac or sacs containing calculi which formed in the gland substance. In a second and less common variety of acquired diverticulum, the prostatic urethra may gradually become distended to form a smooth walled sac as the result of a lodgment of a stone or stones in that portion of the canal. As rarer causes of prostatic pouches, it has been suggested that cysts or abscesses of the gland substance might burst into the urethra and persist as acquired diverticula communicating with the canal. In the anterior urethra acquired diverticula are much more common. The causes are principally trauma of various kinds and periurethral abscesses. Illustrated cases are presented. Regarding the composition of urethral and para-urethral stones it is agreed that stones formed in the prostatic substance are composed of calcium phosphate, calcium carbonate and organic material, and that any of the ordinary kinds of calculi may descend the urinary tract to lodge secondarily in the urethra. The composition of stones found primarily in urethral diverticula is under considerable discussion, as some writers state that such stones must necessarily be wholly of phosphates, whereas others do not see any difficulty in assuming that other than phosphatic calculi may be found in situ.

NATHAN N. CROHN

DIVERTICULOSIS OF THE APPENDIX AND PSEUDOMYXOMA PERITONEI A. J. GARDHAM, C. C. CHOYCE and M. RANDALL, *Brit J Surg* 16 62, 1928

The case reported is that of a diverticulum, the size of a pea, attached to the antimesenteric border of the appendix. Microscopically, the diverticulum protrudes through a cleancut gap in the muscularis, and consists of a single layer of mucous membrane with a covering of granulation tissue, a little fibrous tissue and a few muscle fibers. Gardham notes from the literature that diverticula of the appendix frequently appear to lead to pseudomyxoma of the peritoneum. The diverticulum is found as a result of the destruction of a small area of the muscle coat of the appendix by interstitial abscesses during an attack of appendicitis. When the condition subsides without involvement of the mucous membrane, a diverticulum results. If the diverticulum perforates in cases in which the inflammation subsides without leading to abscess formation, pseudomyxoma peritonei ultimately develop. A case of pseudomyxomatous cyst of the peritoneum following appendicitis is reported. The cyst filled the whole space from the ascending to the descending colon laterally, and from the transverse colon to near the brim of the pelvis below. The perforated tip of the appendix extended into the cyst. The secretion of mucoid material, when the peritoneum becomes involved, persists even after removal of the appendiceal or ovarian cyst.

NATHAN N. CROHN

STAPHYLOCOCCAL SUPPURATIVE NEPHRITIS (CARBUNCLE OF THE KIDNEY)  
B M DICK, Brit J Surg **16** 106, 1928

A review of the literature shows only twenty-seven cases reported. The author adds three cases. The chief characters of the lesion are an acute or subacute hematogenous infection of the parenchyma of one kidney by *Staphylococcus aureus*, the onset of which is frequently preceded by some trauma to the organ. The source of origin is most often a skin lesion, such as a whitlow, boil or carbuncle. The appearance of the kidney varies according to the stage of involvement, the most constant observation is that of multiple areas of necrosis or suppuration confined to one area of the substance of the kidney. Fusion of the suppurative foci gives rise to a honeycomb-like necrotic cavity or a circumscribed encapsulated abscess and a localized enlargement of the affected area. A perinephritic abscess may result, but rupture into the renal pelvis is unusual. Only in one recorded case was the infection bilateral.

NATHAN N CROHN

CALCIFICATION OF THE GALLBLADDER J J ROBB, Brit J Surg **16** 114, 1928

Calcification of the gallbladder is accompanied in 90 per cent of cases by gallstones. The author describes his specimen to be about the shape and size of a large walnut. The serosa was fibrotic, and could be stripped cleanly from the subjacent bony-like layer, the latter averaging 0.2 cm in thickness. The mucosa was absent and was replaced by a layer of lime salts. The author emphasizes the fact that the calcification of the wall was confined entirely to the parts surrounding the calculi and did not extend into the cystic duct. The causal relationship consists in the constant trauma of the muscular wall over the unyielding calculi. This trauma is productive of degenerative changes. Bacterial infection plays an insignificant part in this type. In the infective type which may be unassociated with gallstones, calcification may be the termination of chronic cholecystitis. The process of calcification is differentiated from the deposition of calcium on the mucosa.

NATHAN N CROHN

ENCEPHALO-MYELITIS IN VIRUS DISEASES AND EXANTHEMATA H M TURNBULL, Brit M J **2** 331, 1928

Focal histologic changes extend from the cortex of the brain to the lumbosacral cord in postvaccinal encephalitis. Acute changes noted in persons dying from fourteen to seventeen days after vaccination consist of slight intermittent infiltrations of the leptomeninges, chiefly about the veins, with small and large lymphocytes, plasmacytoid and true plasma cells, large mononuclear leukocytes and endothelial cells. The essential change consists of perivascular and marginal zones of demyelination which form wide sleeves, especially about the veins, and extend along their branches. In the subacute type, the adventitial sheaths are distended with a mosaic of large fat granule cells. Turnbull suggests calling the condition disseminated encephalomyelitis of the postvaccinal type, since it differs from poliomyelitis and lethargic encephalitis and belongs in a group characterized by demyelination as the disseminated myelitis of Westphal and disseminated sclerosis.

GEORGE RUKSTINAT

ENCEPHALO-MYELITIS IN VIRUS INFECTIONS J MCINTOSH, Brit M J **2** 334, 1928

Two theories are advanced to explain the occurrence of postvaccinal encephalitis: first, that the disease is vaccinal in origin, and second, that it is due to the presence of dormant virus stimulated into activity by vaccination, which virus may be that of poliomyelitis, lethargic encephalitis, herpes febrilis or some unknown virus. The arguments McIntosh uses to support the first theory are as follows. Intracerebral inoculations of neurotropic strains of variolous lymph produce an encephalitis in rabbits presenting the main histologic characters of postvaccinal

encephalitis Intravenous injections of neurotropic strains of vaccinia produce focal lesions in the internal organs similar to those found at times in cases of postvaccinal encephalitis and in variola He reports the failure to produce any of the known virus infections of the central nervous system by animal inoculation with material from postvaccinal encephalitis The occurrence of a similar cerebral lesion is reported in a case of encephalitis following smallpox

GEORGE RUKSTINAT

PAINFUL CALCIFIED AND OSSIFIED VAGINAL CORPUSCLES R NOLI and C PELLANDA, *Lyon Chir* **25** 452, 1928

The authors find that calcified and ossified vaginal corpuscles are frequent, having observed them 100 times in three years Usually, symptomless and discovered only accidentally, they are occasionally painful and cause dyspareunia The largest and most painful ones are found in patients with ovarian disturbances due to postpuerperal ovaritis or to genital aplasia following hysterectomy without conservation of the adnexa Local infection is of no importance in their production The location is remarkably constant, and it is definitely lateral at the junction of the upper and middle thirds of the vagina The vaginal wall moves freely over them, and they can be easily removed through a small incision They are usually single, but there may be two or three, in the latter case, one is always larger than the other two The size never exceeds that of a small pea, and is usually much smaller The form is regular, round or slightly elongated, and the consistency is hard The microscopic appearance is constant a vascular fibrous capsule surrounding concentric lamellae of calcified material This material shows the characteristics of bony tissue, with osteoblasts, bone marrow containing blood capillaries, and lymphocyte and plasma cell elements The bodies resemble Pacini's corpuscles and probably originate in degeneration of these sensory organs There may be some significance in the relation between the calcareous degeneration of the sensory end-organs and the attenuation of ovarian function frequently found to be associated with the process

BLATRICE R LOVETT

XANTHOCHROMIA OF CEREBROSPINAL FLUID IN INFANTS J P GARRAHAN, *Rev franç de pédiat* **4** 483, 1928

From the study of 196 specimens of cerebrospinal fluid from 135 new-born infants, Garrahan concludes that xanthochromia of the cerebrospinal fluid is physiologic in the new-born infant Only 20 of 177 specimens of cerebrospinal fluid from infants ranging in age from 1 to 10 days were colorless The intensity of the yellow coloration increases, as a rule, during the first few days and begins to diminish in the second week The presence of even large numbers of erythrocytes in the cerebrospinal fluid of new-born infants is normal The effect of birth trauma on the production of xanthochromia is not clear The yellow color of the cerebrospinal fluid of new-born infants appears to be due to bilirubin Van den Bergh's indirect test almost always gives a positive result, and all new-born infants with icterus have a yellow cerebrospinal fluid Little is known concerning the genesis of the xanthochromia of the cerebrospinal fluid of new-born infants It is not pathognomonic of meningeal hemorrhage

CHANGES IN THE VAGINAL EPITHELIUM DURING MENSTRUATION AND PREGNANCY KARL ADLER, *Arch f Gynak* **134** 505, 1928

The vaginal epithelium is shown to undergo cyclic changes during the child-bearing age analogous to changes occurring in the endometrium The material was divided into three series that obtained from women in the child-bearing age, during pregnancy—post partum and puerperium—and a control series from prepuberty and climacteric patients The cyclic changes were dependent solely on the ovarian function The upper zone of the stratified epithelium formed a differentiated layer which was the forerunner of a still more differentiated layer

of flat cornified cells. The latter layer reached the height of formation during the premenstrual phase, but was absent immediately after menstruation. This layer is termed "functionalis." The cyclic functions were present in patients in whom only the uterus was removed. During pregnancy the zona functionalis was especially well developed by the second month, and was considered diagnostic. Immediately after the delivery, this layer was found to be traumatized and partially removed, but during puerperium, when the ovarian function was held in abeyance and lactation amenorrhea was present, the "functionalis" layer was entirely absent. During childhood and climacterium this layer was likewise absent. The author considered the ovarian hormone the basis for these changes. A. J. KOBAC

FOREIGN BODY IN ABDOMEN J. J. GENKIN, Arch f klin Chir **151** 646, 1928

Following operation for cystic ovary, a movable swelling developed in the abdomen, which proved to be a chylous cyst of the mesentery containing a gauze tampon rolled into a ball.

CEREBRAL HEMORRHAGE IN YOUNG PERSONS OTTO MARBURG, Deutsche Ztschr f Nervenhe **105** 22, 1928

Four cases of cerebral hemorrhage in relatively young persons are reported with no evidence post mortem of either cardiac disease or gross vascular changes. The process was not one of diapedesis, as actual rupture of the vessel wall was seen. Three patients suffered from griplike infection shortly before the hemorrhage, and Marburg found proliferation and swelling of the capillary and arteriolar endothelium. He concludes that obstruction of the capillary bed resulted in an increased vascular pressure and rupture of a vessel. Only one patient seemed to have abnormally thin vessel walls. ROY GRINKER

THE PATHOGENESIS OF MULTIPLE SCLEROSIS H. PETTE, Deutsche Ztschr f Nervenhe **105** 77, 1928

Two acute cases of disseminated encephalomyelitis and one of multiple sclerosis were studied clinically and anatomically. It is concluded that both belonged to the same disease entity, which is caused by some specific neurotropic virus. This conclusion is based on the presence of inflammatory reactions in the cords of both groups. ROY GRINKER

### Pathologic Chemistry

CHEMICAL ANALYSIS OF BLOOD IN PATIENTS WITH SENILE CATARACT C. S. O'BRIEN and V. C. MEYERS, Arch Int Med **42** 376, 1928

In fifty-four patients with cataract, chemical examination of the blood gave essentially negative results, except for an increase of cholesterol in 54 per cent of the cases. HAMILTON R. FISHBACK

THE PLASMA CHLORIDES IN OBSTRUCTIVE JAUNDICE I. S. RAVDIN and M. E. MORRISON, Arch Int Med **42** 491, 1928

There is a constant depression of the plasma chloride value after ligation of the common bile duct and cholecystectomy. After either cholecystectomy or ligation of the bile duct alone depression of the plasma chlorides was not found. HAMILTON R. FISHBACK

THE ESTIMATION OF SILICA IN TISSUES E. J. KING, J Biol Chem **80** 25, 1928

A colorimetric method is described whereby the minute amounts of silica present in animal tissues may be approximated with considerable accuracy. A tabulation is presented, indicating the concentrations of silica ordinarily found

in the lungs, livers and kidneys of healthy dogs and rabbits. The normal silica content of lung tissue of the human being would appear to be about 0.02 per cent, becoming increased to values exceeding 1.8 per cent during silicosis.

ARTHUR LOCKE

THE EFFECT OF AGE ON THE TOTAL AND COMBINED CHOLESTEROL OF THE BLOOD SERUM. R. E. SHOPE, *J Biol Chem* **80** 141, 1928

THE HYPERCHOLESTEROLEMIA OF FASTING AS INFLUENCED BY THE SEPARATE ADMINISTRATION OF FATS, CARBOHYDRATES, AND PROTEINS. *Ibid*, p. 133

CHOLESTEROL ESTERASE IN ANIMAL TISSUES. *Ibid*, p. 127

The blood contains, at birth, little cholesterol and no cholesterol ester. The ester first appears, in quantity, after the ingestion of colostrum and the commencement of the nursing period. During this period the total cholesterol concentration rises rapidly, reaches an early maximum and then declines gradually with the approach of maturity. The decline is more uniform and regular in the male than in the female.

Cholesterol does not appear to have any established function in the process of fat metabolism. The cholesterol content of the blood is not notably increased after maintenance of 48 hours on a diet consisting exclusively of fat, nor is the hypercholesterolemia of fasting animals affected differently by feedings of fat than by feedings of carbohydrate and protein.

The cholesterol ester content of the blood decreases rapidly after death because of the uncompensated activity of the hydrolytic enzyme, cholesterol esterase.

ARTHUR LOCKE

STUDIES ON THE COMPOSITION OF HUMAN MILK. M. BELL, *J Biol Chem* **80** 239, 1928

Consecutive analyses of the breast milk of eighty-eight normal women are reported. The tables presented indicate that the ash and protein content of the milk steadily decreases during the first few days post partum, while the fat and lactose content gradually increases. The influence of supplementary feedings of carbohydrate and fat on the composition and volume of the milk is discussed.

ARTHUR LOCKE

TOTAL SUGAR OF BLOOD AND URINE. THE HYDROLYZABLE SUGAR OF BLOOD. M. EVERETT and F. SHEPPARD, *J Biol Chem* **80** 255, 1928

Leukemic blood contains more hydrolyzable sugar than normal blood, but not enough more to indicate the white cells as its chief source. The sugar is actually present and is not an analytical artefact. It resembles, but may not be identical with, glycogen. (The possible derivation of the sugar from the minute concentration of glycoprotein known to be present in the blood appears not to have been considered.)

ARTHUR LOCKE

OSMOTIC PRESSURE OF BLOOD PROTEINS IN NEPHRITIS. C. L. COPE, *Quart J Med* **22** 91, 1928

The technique of Verney has been employed by Cope to determine the cases of osmotic pressure of the blood plasma proteins in nephritis. In nonedematous nephritis the protein osmotic pressure is unreduced, except slightly just before death, it may, however, be higher than normal, though this rise is not necessarily associated with high blood pressure. In cases of nephritis with edema, a definite fall in protein osmotic pressure occurs and this disappears coincidentally with the subsidence of the edema. In cardiac failure, the protein osmotic pressure may be undiminished when edema is present, or may be found markedly lowered in the absence of demonstrable edema.

CREATINURIA AFTER FRACTURES M HIRST and C G IMRIE, Quart J Med  
22 153, 1928

Hirst and Imrie assert that creatinuria occurs after fracture of bones. The amount of creatine found to be excreted in twenty-four hours in different cases has varied from traces to more than 500 mg. It disappears gradually from the urine as healing takes place and the patient is up and about. The hourly rate of excretion is lowest at night. This creatinuria has been observed in four cases of fractured femurs (all that were studied), in some fractures of the tibia and fibula, in a case of fractures of the pelvis, and in a less degree in several, though not all, cases of fracture of the tibia alone. Administration of thyroid gland increased the output of creatine threefold in a case of fracture of the femur. The hourly rate of excretion was increased during each of the four periods into which the twenty-four were divided, this increase was most marked at night, when, without thyroid, the output was smallest, at other times of the day it was such that the maximum output was shifted from the morning to the evening so as to coincide with the maximum nitrogen output. The increase in the output of creatine preceded any change in the basal metabolism or in the other nitrogenous constituents of the urine. Creatine was not increased, and the uric acid showed only a slight rise. A diuresis was observed in each case as a result of taking thyroid extract, it was most marked and sustained in the case of fracture of the femur, in which the creatinuria was also increased by taking the drug.

## Microbiology and Parasitology

SOME OBSERVATIONS ON THE DEVELOPMENT OF PULMONARY TUBERCULOSIS IN  
LOWER ANIMALS AS COMPARED AND CONTRASTED WITH SIMILAR LESIONS  
IN MAN HERBERT FOX, Am Rev Tuberc 17 435, 1928

The exact homolog of the history and anatomic development of tuberculosis in man is not found among the lower animals, so that great caution must be used in deducing from animal experimentation how the human disease arises. On the other hand, there is a strong similarity between tuberculosis in wild and in domestic *Ungulata*. On the whole, it seems best to consider that each order of animal exhibits a receptivity as a peculiarity. Ordinate receptivity or susceptibility is a distinct feature of the disease tuberculosis. Zoological family receptivity is likewise important, perhaps more so than is ordinate. Some families of primates are more susceptible than others, and this is also true in the families of the orders *Carnivora* and *Rodentia*. *Ungulata*, to which the domestic cow belongs, show the same type of morbid lesions in all the families, and it is believed that all families are about equally susceptible, even though some, *Tapiridae*, have not been seen with the disease by the author. Lower animals behave in a definite manner when they meet the tubercle bacillus for the first time. There is no true healing, as occurs in man. Certain varieties of animals, the kangaroos, for example, do not seem to have receptivity for the bacillus. In the face of the facts learned from animals, the thought that the human being reacts in a peculiar characteristic manner because he has a definite type of reactivity cannot be dismissed until the identical reaction of the domestic and wild bovine is explained. *Carnivora* react like human beings, certain primates react like youthful human beings and other primates do not react at all. It seems, therefore, that the individual peculiarity of an order, family or genus must play a large rôle in the inception, development and result of tuberculous infection. Infection early in life and recovery therefrom will not explain chronic ulcerative tuberculosis in carnivores or chronic calcareo-caseous lesions in bovine, nor will it satisfactorily settle variations in dispositions in families of the same order. It seems, therefore, that human phthisis is a specific type of receptivity for the bacillus and not the result of acquired immunity, and the calcareo-caseous morbid anatomy of bovine is peculiar to them, and so on through the groups. These data also strongly support the thought that infection may occur at any age and that the hygiene of animals must guard adults as well as young.

H J CORPER

THE REACTIONS OF THE WHITE BLOOD CELLS OF THE RABBIT ON INOCULATION WITH LEPROSY BACILLI EDGAR JONLS and W O TIRRELL, JR, Am Rev Tuberc **17** 522, 1928

Leprosy bacilli, when given in large amounts, stimulate the hematopoietic tissues of the rabbit to a temporarily increased production of both lymphocytes and monocytes. The stimulation occurs in spite of the fact that a definite infection of the animals did not occur.

H J CORPER

THE REACTIONS OF THE WHITE BLOOD CELLS OF THE RABBIT FOLLOWING INOCULATION WITH SMEGMA BACILLI LEO SCHWARTZ, JR, and R S CUNNINGHAM, Am Rev Tuberc **17** 537, 1928

The object of the experiments was to determine whether the reaction of the rabbit to smegma bacilli had any common factors with those seen after inoculation with virulent tubercle bacilli. The results are categorically definite in showing that there is at least one clearcut similarity in the two types of infection, that is, the increase in the number of the monocytes of the circulating blood and tissues, and the modification of these in the direction of the so-called epithelioid cells. That the smegma bacillus is not especially toxic is amply indicated by the long course pursued by some of these animals without any change in the blood counts; however, when sufficiently large numbers of micro-organisms were injected the animals developed massive lesions of the lungs and other tissues and finally died from the effects of the lesion. In studying the epithelioid cells it was noted that while the bacilli had been phagocytosed in large numbers, most of them were surrounded by neutral red vacuoles, a possible beginning degeneration of bacilli.

H J CORPER

TUBERCULOUS INFECTION OF THE LUNG IN EARLY INFANCY JEROME L KOHN, Am Rev Tuberc **17** 565, 1928

A case is presented of tuberculosis in an infant, aged 12 weeks, who was probably infected six weeks before the onset. The Pirquet reaction was positive at 12 weeks, and the first symptoms appeared at 9 weeks of age. The clinical picture simulated that of obstruction by a foreign body or thymic compression. The development and recession of the disease was noted by means of serial roentgenograms. The primary focus (Ghon) was first observed when the child was 3 years and 2 months old. The source of infection was never definitely ascertained. The prognosis of tuberculosis even in early infancy is not necessarily fatal. This child developed normally and was in excellent health more than five years after it first came under observation.

H J CORPER

TUBERCULOSIS OF THE ANTERIOR MEDIASTINAL LYMPH NODES RICHARD C BUCKLEY, Am Rev Tuberc **17** 583, 1928

Tuberculosis involving the anterior mediastinal lymph nodes is uncommon. Among 115 cases of pulmonary tuberculosis the author observed the condition in 2 cases, both of which were unusual. In the first case one of the lymph nodes was attached to the parietal pericardium and had ruptured into the pericardial sac, and a tuberculous pericarditis resulted. In the second case, which is reported, the condition simulated an aneurysm of the aorta or a mediastinal tumor.

H J CORPER

MODERN CONCEPTS IN THE PATHOLOGY OF TUBERCULOSIS MAX PINNER, Am Rev Tuberc **17** 601, 1928

The author points out that it is not in the nature of this analysis to arrive at conclusions but notes that a few points, however, are clearly brought out. 1 The necessity of a terminologic understanding is paramount. 2 In human



pathologic changes, at least, the relation of allergy to immunity is obscure 3 The allergic condition of the host cannot satisfactorily explain the occurrence of productive and of exudative lesions at the site of reinfection or metastasis 4 Productive and exudative lesions, immunologically speaking, are not necessarily antagonistic either may heal, and either may progress 5 The immunologic conditions under which healing or progression occurs are not well understood 6 Important, though not exclusive, factors which determine the productive or exudative development of a lesion are hypersensitiveness and resistance to bacilli and localization and dosage of bacilli, a number of secondary factors must be considered

H J CORPER

THREE CASES OF STREPTOCOCCIC PUERPERAL INFECTION WITH UNUSUAL LESIONS JOHN W HARRIS and J HOWARD BROWN, Bull Johns Hopkins Hosp **43** 26, 1928

Three unusual cases of streptococcic puerperal infection are reported 1 A case of miliary abscesses of the uterine wall in which hysterectomy was performed and in which the streptococcus was recovered from the uterine cavity 2 A case of postabortal, bilateral thrombophlebitis in which the affected veins were ligated and in which identical streptococci were recovered from the uterine cavity and blood stream 3 A case of puerperal endometritis, extensive encapsulated peritonitis and embolic pneumonia in which the same streptococcus was recovered from the uterus and from the peritoneal and pulmonary exudates The streptococci found in these three patients were of three different strains, as shown by the differences in fermentation reactions According to Holman's classification, the organism from the first case was *Streptococcus infrequens* and those from the last two cases were *Streptococcus pyogenes* Further differentiated by Brown's classification, the first two streptococci were atypical members of the *infrequens* and *pyogenes* groups, while the last was a typical *Streptococcus pyogenes*

AUTHORS' SUMMARY

THE BACTERIAL CONTENT OF THE VAGINA AND UTERUS ON THE FIFTH DAY OF THE NORMAL PUERPERIUM JOHN W HARRIS and J HOWARD BROWN, Bull Johns Hopkins Hosp **43** 190, 1928

In thirty uteruses cultured on the fifth day of the normal afebrile puerperium, only ten were found sterile, but none contained streptococci Vaginal cultures taken at the same time showed the presence of aerobic and anaerobic alpha and gamma streptococci in twenty-four of the thirty patients, but the aerobic, beta-hemolytic streptococcus, which is the etiologic factor in the majority of fatal cases of puerperal infection, was not present in any of the patients studied

AUTHORS' SUMMARY

EXPERIMENTAL STREPTOCOCCUS NECROSIS OF THE LIVER R N NAY, J Clin Investigation **6** 27, 1928

Intravenous injection into rabbits of bacteria-free filtrates of a certain strain of *Streptococcus scarlatinae* resulted in death The toxin was relatively thermostable and could be neutralized by scarlet fever antitoxin It was found in only one of five strains of *S. scarlatinae* The most marked pathologic change in the killed rabbits consisted of areas of necrosis of the liver, similar to toxic necrosis of the liver seen in human cases Frequent mitoses in the suprarenals and kidneys suggested damage to those organs

AUTHOR'S SUMMARY

HYDROLYSIS OF BACTERIAL PROTEIN DURING LYSIS BY BACTERIOPHAGE D M HETLER and J BRONFENBRENNER, J Exper Med **48** 269, 1928

During the process of lysis by bacteriophage, there is an appreciable increase in the amount of free amino-acid present in the culture The increase of free amino-acid is due to hydrolysis of bacterial protein

AUTHORS' SUMMARY

TOXIN PRODUCTION BY NORMAL AND BY PHAGE-RESISTANT SHIGA DYSENTERY  
BACILLI RALPH S MUCKENFUSS and CHARLES KORB, J Exper Med  
48 277, 1928

The production of exotoxin and of endotoxin by normal Shiga dysentery bacilli and by strains resistant to Laudman phage was found to be the same. The presence of phage did not alter toxin production by the resistant organism.

AUTHORS' SUMMARY

THE INFLUENCE OF CHOLESTEROL ON EXPERIMENTAL TUBERCULOSIS RICHARD  
E SHOPE, J Exper Med 48 321, 1928

Cholesterol, administered intraperitoneally in these experiments, definitely prolonged the lives of tuberculous guinea-pigs when the infection was of an acute type produced by inoculation with a small dose of virulent human type organisms. Intraperitoneally administered cholesterol did not definitely prolong the lives of tuberculous guinea-pigs when the infection was of the chronic type produced by the injection of a small dose of human type tubercle bacilli of relatively low virulence, or when the infection was more acute owing to the injection of a large dose of organisms of low virulence. It had no beneficial effect on an acute type of infection produced by the bovine type organism. Cholesteryl chloride, cholesteryl toluide, cholesteryl anilide, sodium cholesterol sulphate and quinine cholesterylate did not significantly prolong the lives of tuberculous guinea-pigs. Sodium cholesterylate, in optimal dosage, definitely prolonged the lives of tuberculous guinea-pigs. There was a significant shortening in the duration of life of tuberculous guinea-pigs subjected to the trauma of intraperitoneal injection and repeated handling as compared with tuberculous guinea-pigs that were not handled or traumatized by intraperitoneal injections.

AUTHOR'S SUMMARY

RECIPROCAL EFFECTS OF CONCOMITANT INJECTIONS LOUISE PIARCE, J Exper  
Med 48 363, 1928

An experiment is reported in which was studied the effects of a concomitant vaccinal infection and of vaccinal immunity on the reaction to syphilis in rabbits induced by intracutaneous inoculation. The results obtained showed that the reaction was modified by both conditions. A vaccinal infection initiated at the time of syphilitic inoculation was associated with a defensive reaction of lessened efficiency, the ensuing syphilis being more severe than in control animals. A state of vaccinal immunity present at the time of syphilitic inoculation was associated with a reaction of heightened efficiency, the ensuing syphilis being mild. These results are in harmony with those obtained in other experiments in which the intratesticular route of syphilitic inoculation was employed.

AUTHOR'S SUMMARY

THE ACTION OF THE LEVADITI STRAIN OF HERPES VIRUS AND OF VACCINE  
VIRUS IN THE GUINEA-PIG PETER K OLITSKY and PERRIN H LONG,  
J Exper Med 48 379, 1928

Repeated intraperitoneal injections in guinea-pigs of the Levaditi strain of herpes virus do not cause any evidences of infection, yet induce immunity to strong strains of herpes virus.

AUTHORS' SUMMARY

STUDIES ON INDIFFERENT STREPTOCOCCI C H HITCHCOCK, J Exper Med  
48 393 and 403, 1928

Serologic study of a large number of strains of indifferent streptococci has revealed the existence of a large homogeneous group to which the designation type 1 has been applied. It is recognized that members of type 1 are not necessarily identical, and that further division into subtypes may be feasible. All strains of

type 1 ferment inulin and salicin. The remaining strains are referred to as belonging to group X. They are distinguished only by their failure to react strongly with type 1 serum. While at present this group must be regarded as quite heterogeneous, further work may reveal the presence of other as yet undefined types now included within its limits. The organisms of this group vary in their fermentative reactions with both inulin and salicin. Indifferent streptococci occur in comparatively the same abundance in the throats of patients suffering from rheumatic fever or early in convalescence from the disease as they do in those who have recovered from the disease, or in those of patients suffering from other diseases. There is a slightly increased incidence of these micro-organisms in the throats of hospital patients as compared with those of normal persons. Type 1 occurs with comparatively equal frequency and abundance in the throats of all four classes of patients studied.

AUTHOR'S SUMMARY

FURTHER EXPERIMENTS WITH THE INTRADERMAL PNEUMOCOCCUS INFECTION IN RABBITS. KENNETH GOODNER, J. Exper. Med. **48** 413, 1928

The analogy between intradermal infection in rabbits with pneumococcus type 1 and human lobar pneumonia is emphasized. As this disease progresses, the amount of antiserum necessary for cure progresses definitely as if there occurred a progressive accumulation of some toxic or antagonistic substance. The effect of anti-pneumococcus serum in intradermal pneumococcus infection in rabbits may prove to be of value in standardizing antipneumococcus serum. Rabbits that recover from the normal course of intradermal disease have a pronounced but not permanent immunity. Immunity may also be conferred by single and multiple vaccination.

AUTHOR'S SUMMARY

THE RÔLE OF STREPTOCOCCI IN EXPERIMENTAL POLIOMYELITIS OF THE MONKEY. PERRIN H. LONG, PETER K. OLITSKY and FRED W. STEWART, J. Exper. Med. **48** 431, 1928

The results of the experiments point to the introduction of streptococci as contaminants into cultures during the grinding of tissues. It was found that while streptococci in some cultures occurred in pure growth in others they were mixed with other ordinary bacterial forms which also often were found in pure culture. Any etiologic relation of the streptococci to poliomyelitis could not be determined.

AUTHORS' SUMMARY

STUDIES OF ACUTE RESPIRATORY INFECTIONS. W. C. NOBLE, JR., and D. H. BRAINARD, J. Prev. Med. **2** 313, 1928

In healthy persons, an anaerobic gram-negative coccus identical with or similar to *M. gazogenes* occurred so frequently as to constitute part of the normal flora of the nasopharynx, it was often found in large numbers and was twice the predominating species. A gram-negative bacillus was encountered in one healthy subject, but only in small numbers. In colds the gram-negative coccus occurred with little change in frequency, but with an average percentage incidence slightly above that observed in healthy persons. Four gram-positive cocci were isolated from three subjects and two gram-positive bacilli from one. Three other species of gram-negative bacilli were found, all differing from the organism encountered in the normal subject. The gram-positive cocci and the gram-positive and gram-negative bacilli occurred infrequently and in small numbers.

AUTHORS' SUMMARY

EMPHYSEMA IN A CHILD THREE DAYS OLD. GLADYS H. DODDS, J. Obst. & Gynec. Brit. Emp. **35** 131, 1928

A primipara having a moderately prolonged labor and membranes ruptured six hours prior to delivery gave birth to a 8½ months, poorly developed child,

weighing 2,600 Gm. The child became progressively worse and died after eighty-seven hours. Free pus was found in both pleural cavities, and the culture showed a mixed growth of pneumococcus and staphylococcus. The lung showed extensive pneumonia. Among other factors, the prolonged period of ruptured membranes is considered as a source whereby the organisms in the vaginal tube are allowed free access to the fetus, thus permitting aspiration by the fetus.

A J KOBAR

PULMONARY AND BRONCHIAL GLAND TUBERCULOSIS IN INFANCY AND CHILDHOOD P. F. ARMAND-DIHIIL and C. LESTOCQUOY, *Tubercle* 9 359, 1928

Tuberculous bronchial glands are always enlarged. These enlargements frequently occur in the middle of the mediastinum. Their shadows can rarely be observed in the x-ray plate because they are usually masked by the shadows of the heart, aorta and the superior vena cava. The so-called perihilar shadows are not produced by the glands, for these can give rise only to juxtatracheal shadows. The primary inoculation (chancre d'inoculation) demonstrable in nearly every case after patient search of postmortem sections is only exceptionally detectable in the x-ray picture. A good x-ray plate (a fluoroscope is insufficient) may reveal the presence of miliary tuberculosis early in the course of the disease, often before any other characteristic signs or symptoms have appeared. Pictures taken during the early stages of the disease may show localized lobar shadows persisting for months. An almost identical shadow can be given by primary hepatization, secondary hepatization caseation and even by splenopneumonia, while sections show that what may have been considered a perihilar condensation in reality corresponds to the first stages of a lobar bronchopneumonic invasion. Roentgenography, in series, shows that in some cases the shadows can progressively disappear, even though it has been possible to demonstrate tubercle bacilli in the sputum. The cases in which healing occurs are rare, and progression is common.

H J CORPLER

INTESTINAL TUBERCULOSIS M. J. STEWART, *Tubercle* 9 409, 1928

There are only two important varieties of intestinal tuberculosis: one secondary and usually a complication of pulmonary phthisis, the other, hyperplastic tuberculosis, apparently in most cases a primary infection. In typical examples, the pathologic process in these two lesions varies enormously. Secondary tuberculosis is usually frankly ulcerative and shows at the advancing margin the characteristic histology of the tubercle follicle with abundant giant cell systems and caseation. There is little reactive fibrosis, and the muscular coat is rarely penetrated completely. As a rule the ulceration is widespread, extending upward and downward from the seat of election, the ileocecum. In contradistinction to the hyperplastic type, secondary intestinal tuberculosis rarely gives rise to serious obstruction. Strictures, when they occur, are often multiple, and are usually situated in the small intestine. Primary hyperplastic tuberculosis of the intestine is rare in America and more prevalent in European countries. The author reports twenty-one cases of his own in which the treatment was surgical. The lesion is essentially proliferative, and ulceration, while often or even usually present, is not as a rule the conspicuous feature which it is in the secondary type. The walls of the affected portion of the intestine become greatly thickened and hardened, all coats being involved. Of the twenty-one cases, eighteen were histologically tuberculous, two showed tubercle follicles only in the associated lymph glands, while in one tuberculosis was entirely absent. Hyperplastic tuberculosis is a disease of the ileocecal region, it is usually confined to the last foot of the ileum, the ileocecal valve, the cecum or the ascending colon, any or all of which may be involved. Stenosis is most frequent at the lower end of the ileum but occurs in the ascending colon. Occasionally there is much epithelial proliferation, with the formation of true adenomatous polyps. Occasionally, the appendix is involved. Three factors are suggested in explanation of the peculiar tuberculous lesion in primary hyper-

plastic tuberculosis (1) a fairly high grade of immunity, (2) infection by small numbers of bacteria, and (3) infection by bacteria of low virulence, in many cases bovine

H J CORPER

FUSOSPIROCHETAL DISEASES OF THE LUNGS DAVID T SMITH, *Tubercle* 9 420, 1928

Various studies indicate that pulmonary gangrene, most cases of pulmonary abscess, certain types of unresolved pneumonia, and bloody bronchitis, putrid bronchitis and chronic bronchiectases are not separate disease entities but different manifestations of infection with an anaerobic group of organisms acting in symbiosis. This group of organisms include (1) spirochetes (*Treponema microdentium*, *Treponema macrodentium*, *Spirochaeta vincenti* and *Spirochaeta bronchialis*), (2) fusiform bacilli, (3) vibrios, and (4) cocci. These forms are constantly present (1) in the washed pulmonary sputum and (2) in the pulmonary tissue at necropsy, and have been found (3) in the pulmonary tissues of animals dying of the disease transmitted to them by injection of the sputum from patients with abscess and bronchiectasis. Similar organisms are normally present in the gums of patients with pyorrhea, and these pyorrhea organisms will produce typical pulmonary abscesses when introduced into the trachea of mice, guinea-pigs, rabbits or dogs. The patients' own gums are probably the most common source of infection, although infection of the pharynx with Vincent's angina may be a source of danger to others as well as to the patient. Rest in bed, postural drainage and arsenical therapy in the early stages, and skilful surgical intervention in the resistant cases will produce a fairly good percentage of cures. Proper oral hygiene is the most important preventive factor.

H J CORPER

YEASTS AND SPRUE F P MACKIE and G D CHITRE, *Indian Medical Research Memoir* 11, Supplement to *Indian J M Research*, 1928

In Bombay, *M. psilosis* (Ashfordi) has been found present in 40 per cent of cases of sprue, it has been found in similar frequency in intestinal diseases (not sprue) in other miscellaneous diseases, and in healthy men and animals, there is no evidence to show that it, or any other of the yeasts studied, has any causative relation to sprue.

AUTHORS' SUMMARY

EXPERIMENTAL NOCARDIASIS PIERO REDAELLI, *Bol dell 'Istituto Sieroterapico Milanese* 7 121, 1928

The author, making use of *Nocardia sanfelice* N. Sp., studied the primary infection and the cellular factor of natural immunity in receptive animals (guinea-pigs, rabbits), in less receptive animals (dogs) and in refractory animals (fowls).

In receptive, less receptive and refractory animals, the method of the development of the inflammatory process is the same. It is possible to distinguish clearly the diverse moments of the process of reaction, at first of an exudative character and which culminates in the formation of the characteristic and typical nocardiac granule. The stages through which the parasite passes are different just as the moments of the inflammatory reaction of the organism are different. The inflammatory productive phenomena are accompanied by degenerative processes.

The fundamental difference between cellular defense in receptive, less receptive and refractory animals lies in a more ready reaction on the part of the less receptive and refractory organisms, in the acceleration of the rhythm during development of the different periods of the inflammatory process, in a more rapid attainment to that stage in which the specific systems of defense are developed and, therefore, in a more rapid exhaustion of the disease in refractory animals and in the passage of the disease to the chronic state in animals which are less receptive.

A J SALLE

THE CHANGES OF NEUTROPHILE GRANULES IN INFECTIOUS DISEASES ANTOINE SANDELS, *Jahrb f Kinderh* **120** 196, 1928

On the basis of the demonstrations of Mommer that normal neutrophilic leukocyte granules disappear at a  $pH$  of 5.35 while those which are formed by the influence of the toxins of certain infectious diseases (scarlet fever, croupous pneumonia) do not, Sandels studied the character of the occurrence of such pathologic granules in instances of diphtheria, measles, grip, angina follicularis, typhus abdominalis, dysentery, tuberculous meningitis and influenzal meningitis. In all of the acute infectious diseases, the "toxic" granules made their appearance some time after the onset of the disease, reaching a maximum in from five to nine days. In some instances as much as 80 per cent of the leukocytes contained these pathologic granules. Sandels pointed out that a fall in the absolute count of the leukocytes goes hand in hand with an increase in the "pathologic granules." He also observed that there was a decrease in number accompanying an increase in the severity of the disease and before death. He regards them as the result of a physico-chemical process, a probable coagulation or precipitation of the neutrophilic protoplasm in the circulating blood.

FRANK R. MENNE

METAL SALT THERAPY AND PROPHYLAXIS IN TUBERCULOSIS L. E. WAIBUM, *Ztschr f Tuberk* **51** 209, 1928

Rabbits were infected intravenously with 0.0001 mg. of moist bovine bacilli of high virulence. The metal salt therapy was started thirty-three days following the infection. The following metals and salts were tested: Cadmium, manganese, "cadmium-complex," cerium, barium, aluminum, lanthanum, molybdenum, platinum, beryllium, zinc, indium, silver, mercury, arsenic, erbium, tungsten, ruthenium, selenium, gold chloride, sodium aurothiosulphate in large and small dosage, 4 amino-2 auro-thiophenol carbonic acid and sodium fluorid. The best therapeutic action was found in cadmium and manganese. Definite but less effective action was found in cerium, barium, aluminum, lanthanum, molybdenum and platinum. All the other materials were not therapeutically active. Similar experiments were performed on tuberculous guinea-pigs. All animals, with the exception of one, died of tuberculosis. Normal rabbits and goats were treated with cadmium and infected later. They all developed tuberculosis, but this was of a benign type and healed finally. Guinea-pigs could not be protected against a later infection, but their natural resistance toward tuberculosis was definitely increased.

MAX PINNER

DISINFECTION WITH FORMALDEHYDE IN AQUEOUS SOLUTION AND IN GASEOUS FORM IN TUBERCULOSIS E. BERGIN, *Ztschr f Tuberk* **51** 306, 1928

Tubercle bacilli were killed in sputum exposed to a highly concentrated formaldehyde water vapor at a temperature of from 62 to 63 degrees for two hours.

MAX PINNER

THE NUMBER OF BACILLI IN CULTURES OF TUBERCLE BACILLI W. BLUMENBERG and H. WIENING, *Ztschr f Tuberk* **51** 417, 1928

Even suspensions of tubercle bacilli, which are free of clumps, can be obtained by using a 15 molar solution of sodium oxalate to which a sufficient amount of sodium carbonate is added to obtain a  $pH$  of from 8.5 to 8.7. The action of the sodium oxalate is due to two factors, namely, the decrease of surface tension and the precipitation of calcium compounds. Suspensions prepared by this diluent were counted in Burker's counting chamber. The counting was done in the dark field. The entire apparatus and the solutions must be specially prepared so as to be completely free of formed elements with the exception of the bacilli. Numerous counts indicate that the number of bacilli contained in 1 mg. of moist bacillary mass

is always above one billion and may be as high as four billions. The number of individual cells depends on the nature of the strain, on the medium on which it is grown and on the age of the colony.

MAX PINNER

INVESTIGATION OF FORMS OF *B. COLI* OCCURRING IN MAN OTTO MIKKELSEN, Copenhagen, Kandrup & Wunsch, Printers, 1927, Pp 150 In Danish

The author studied 185 strains from the urinary tract of 180 patients as well as strains from normal feces. No fixed relation was found between urinary infections and fermentative or serologic types of *B. coli*. It appears that certain definite fecal strains under suitable conditions may cause urinary infections.

### Immunology

RESPIRATORY IMMUNITY IN RABBITS CARROLL G BULL and C M McKEE, Am J Hyg 8 477, 1928

Observations are given which emphasize the fact that bacteria and their specific products readily pass through the mucous membrane of the upper air passages. Systemic effects always were found to follow the presence of bacteria on the mucous membrane of the upper air passages in rabbits, although local effects were not always demonstrable.

PEARL ZEEK

RESPIRATORY IMMUNITY IN RABBITS G HOWARD BAILEY and S C CHENG, Am J Hyg 8 485, 1928

Injection into rabbits of heat-killed cultures of *Bacterium leprosepticum* exerted a marked protective influence against that organism. Rabbits with subcutaneous or joint abscesses appeared to be immune to intranasal or pulmonary infection with that organism. Previous carriers were more resistant to subsequent inoculation of the organism. The results of the experiments varied in some instances as the ordinary mucoid strain of *Bacterium leprosepticum* or the virulent D type of that organism was used.

PEARL ZEEK

RESPIRATORY IMMUNITY IN RABBITS C G BULL and C M McKEE, Am J Hyg 8 723, 1928

Pneumococci are able to "settle," live and multiply on the nasal mucosa of normal nonimmunized rabbits for only a limited time. Immunized rabbits do not become carriers. The carrier state ends with the appearance of antibodies in the body fluids.

*Bacillus bronchisepticus* may be carried for a long time, although the carrier state stimulates the production of antibodies within a few days. Immunized rabbits may readily become carriers.

The difference in the effect of immunity on the carrier state in the case of these two organisms is thought possibly to be caused by a difference in the nature of the antibodies stimulated by them.

PEARL ZEEK

PATHOGENESIS AND RECOVERY IN ERYSIPELAS T FRANCIS, JR., J Clin Investigation 6 221, 1928

Skin reactions were studied in patients at intervals, and the blood in different stages of the disease was tested for toxin by injecting serum into the skin of susceptible and resistant persons. Neutralization tests were made with the serum of patients and the specific toxin. The results are regarded as indicating a tendency toward increasing reactivity of the skin during convalescence, the absence of a demonstrable toxin in the blood of patients in the acute stage of the disease, and the neutralization of erysipelas toxin by the serum of most patients in the acute stage of the disease with the loss of this power during convalescence.

H R FISHBACK

SEROLOGIC TYPES OF *CLOSTRIDIUM TETANI* GEORGE E. COLLMAN and JANET B. GUNNISON, J. Infect. Dis. **43** 184, 1928

The results of agglutination and absorption tests indicate that there are at least nine distinct serologic types of *Clostridium tetani*.

#### AUTHORS' SUMMARY

RHEUMATIC FEVER. 2 ALLERGIC REACTIONS WITH A TOXIN-PRODUCING STRAIN OF THE NONMETHEMOGLOBINFORMING STREPTOCOCCUS ISOLATED FROM RHEUMATIC FEVER. KONRAD E. BIRKHAUG, J. Infect. Dis. **43** 280, 1928

Guinea-pigs and rabbits sensitized to the nonmethemoglobin-forming streptococcus isolated from patients with rheumatic fever may be rendered cutaneously hypersensitive to filtrates of cultures of this organism. A brief period of specificity in the sensitive state is recorded. This period is shortly followed by a sensitive state that is nonspecific. During this phase of the cutaneous reactions, the allergenic property of the filtrate can be nullified completely with specific antisera. After the end of the cutaneous allergy of this first phase, continued sensitization of the animals with living nonmethemoglobin-forming streptococci produces the reappearance of cutaneous allergy. During the second phase, the reactions of allergy are nonspecific and the allergic principle of the filtrate is nonneutralizable with specific antisera. For this phase, filtrates heated at 98 C. for four hours are not inactivated as allergic substances. Heterogeneity in the cutaneous responses of patients with rheumatic fever to filtrates of the nonmethemoglobin-forming streptococcus and to certain strains of *Streptococcus viridans* might be explained on the basis of prolonged sensitization to any one dominant strain of the non-hemolytic streptococci. Desensitization of bacterially hyperallergic guinea-pigs and rabbits was accomplished during the second phase of cutaneous allergy by intracardial or intravenous injections of bacterial filtrates.

#### AUTHOR'S SUMMARY

ANTIGENIC ANALYSIS OF STRAINS OF *BACILLUS TYPHOSUS*. LION C. HAVENS, J. Infect. Dis. **43** 335, 1928

The antigenic identity of strains of *B. typhosus* has been studied by agglutinin absorption, complement fixation and bactericidal activity. The greatest differences between strains were obtained by agglutinin absorption with fractional doses. Complement-fixation and bactericidal tests indicated only minor differences between the strains tested.

Agglutinin absorption is probably the most sensitive method of bringing out differences in antigenic composition. The results indicate that the method is more delicate than practical uses demand. The suitability of a particular culture for the Widal test or for vaccine cannot be definitely determined by means of these experiments, but they indicate that complement fixation and bactericidal tests conform most closely to the empirical evidence gained from practical application in the field.

#### AUTHOR'S SUMMARY

BIOLOGIC AND SEROLOGIC STUDIES OF *STREPTOCOCCUS CARDIOARTHRTIS*. WILLIAM A. KREIDLER, J. Infect. Dis. **43** 415, 1928

The 107 strains of *Streptococcus cardio-arthritidis* studied, exhibited a marked uniformity in their biologic reactions. All fermented dextrose, sucrose, inulin, salicin and raffinose, none fermented mannitol. Twenty-one strains (19.6 per cent) failed to ferment lactose and failed to produce acid in milk. None liquefied gelatin or produced indol.

Antigens prepared from each of the strains were agglutinated by a monovalent antiserum of *S. cardio-arthritidis* in dilutions high enough to indicate that these strains fall into a definite serologic group and that group agglutinins play but a small part in the results obtained. When the foregoing facts are considered,



there seems to be reason for the belief that these micro-organisms biologically and serologically form a compact species of streptococci. The failure of some of the strains to ferment lactose and the difference in the agglutinability of the strains, suggest that there may exist, within the species, immunologic subtypes of *Streptococcus cardio-arthritidis*.

AUTHOR'S SUMMARY

THE APPROXIMATION OF THE TOXICITY OF DIPHTHERIA TOXIN IN VITRO  
ARTHUR LOCKE AND E. R. MAIN, J Infect Dis **43** 420, 1928

A simple, practicable method is reported, whereby the  $L_0$  titer of an unmodified diphtheria toxin may be predicted, in vitro, with an accuracy of from 85 to 95 per cent. The method is based on the use of a formula correlating the properties of toxicity and antitoxin-binding avidity. It consists of a modified flocculation titration, wherein the latter property is evaluated in terms of  $L_1$  titer and "unit flocculation time," the results being converted into toxicity units by reference to the basic formula.

AUTHORS' SUMMARY

SENSITIZATION AND IMMUNIZATION WITH BACTERIOPHAGE IN EXPERIMENTAL  
PLAGUE ARTHUR COMPTON, J Infect Dis **43** 448, 1928

Treatment of experimental plague by subcutaneous injection of a weak phage after infection is without any curative effect. The prophylactic use of such a phage, however, is occasionally attended by a partial protection, sufficient to prolong life but insufficient to save the animal. The partially protected animal does not die of phage-resistant, but of ordinary phage-susceptible, plague bacilli. Better prophylaxis results from two interspaced subcutaneous inoculations of antiplague bacteriophage than from one. Actually, after two inoculations of phage, at six days' interval, 40 per cent of such highly susceptible animals as mice showed absolute immunity. No immunity whatever, but instead increased susceptibility to infection followed the prophylactic use of stock vaccine under similar conditions. Marked hypersensitivity to infection (sensitization) attends a limited proportion of the animals undergoing phage immunization, their early deaths being apparently part of a process the end-result of which is the establishment of absolute immunity among a certain other proportion of the animals.

Weak phage, subcutaneously inoculated, is apparently suppressed by the tissues, in this respect recalling the suppression of a weak herpesencephalitis virus by the brain tissue of the rabbit or guinea-pig. Failure to detect the presence of any active phage in the excreta and blood of animals exhibiting absolute immunity after phage inoculations, leads to the tentative conclusion that the immunity in question is probably fundamentally antibacterial rather than protobiotic in nature.

AUTHOR'S SUMMARY

THE OPSONIFICATION TEST FOR THE RAPID IDENTIFICATION OF THE STREPTOCOCCUS OF SCARLET FEVER KATHARINE M. HOWELL and MARIE WERNER, J Infect Dis **43** 525, 1928

Although the opsonification test for the identification of scarlet fever streptococci is not absolutely specific in our series, it nevertheless offers a rapid, valuable aid in the diagnosis of scarlet fever.

AUTHORS' SUMMARY

THE UNITS OF PROTECTIVE ANTIBODY IN ANTIPNEUMOCOCCUS SERUM AND ANTIBODY SOLUTION LLOYD D. FELTON, J Infect Dis **43** 531, 1928

A method is outlined for the standardization of antipneumococcus serum and pneumococcus antibody concentrate. The unit is that fraction of a cubic centimeter of serum or antibody (or dilution) which will protect against one million fatal doses of an eighteen hour serum broth culture of such virulence that from three to ten organisms injected intraperitoneally into a mouse result in death in from thirty-

six to forty-eight hours. In practice 500,000 fatal doses of organisms—0.5 cc of 1:200 dilution of an eighteen hour serum broth culture in which from three to ten organisms, as estimated by the plate method, are present in a 1:100,000,000 dilution of culture—are used against dilutions of test serum or antibody in a geometric series. By maintaining these units, the reciprocal of the dilution protecting two of three mice represents the number of units in 1 cc of serum or antibody.

AUTHOR'S SUMMARY

CONCENTRATION OF PNEUMOCOCCUS ANTIBODY LLOYD D. FELTON, J. Infect. Dis. **43** 543, 1928

A method for the concentration of the protective substance in antipneumococcus horse serum has been given. Anhydrous sodium sulphate in 20 per cent concentration is used as precipitating agent. The usual technic for filtering and dialyzing the "cake" is employed. The contents of the sac, euglobulin, pseudoglobulin and protective substance, are adjusted to  $pH$  4.6 to 4.8, at which point a precipitate is formed containing an inert protein (euglobulin?) along with a quantity of lipoids. This precipitate is removed and the clear supernatant (pseudoglobulin, protective substance, some euglobulin and albumin) is adjusted to  $pH$  6.8, and diluted 4 or 5-fold with cold distilled water. A white precipitate is thrown down containing practically all the protective substance present in the original serum. This precipitate dissolves readily in sodium chloride, is high in protective power, and for intravenous injection, is practically free from severe chill-producing characteristics.

AUTHOR'S SUMMARY

IMMUNOLOGICAL INVESTIGATIONS ON TROPICAL SPRUE IN PORKO RICO CHARLES WEISS and FRANCISCO LANDRON, J. Infect. Dis. **43** 557, 1928

The isolation of *Monilia psilosis* from the feces is greatly facilitated by the use of glycerol and bile to inhibit the growth of common fecal bacteria. With this technic the fungus has been obtained from a large percentage of both cases of sprue and control subjects. *M. psilosis* grows in both liquid and solid mediums over a wide  $pH$  range with an optimum of  $pH$  7 in infusion broth. In liquid mediums of low  $pH$ , growth brings a progressive alkalinity approaching  $pH$  8, the apparent optimum for survival. These observations are not in harmony with the idea that an increased acidity of the intestinal contents favors the establishment of the fungus. Intravenous injection of *M. psilosis* kills rabbits in from a few minutes to forty-eight hours, the time depending on the dose. In the later deaths visceral embolic lesions containing the fungus are found. *M. albicans* and a cryptococcus of blastomycosis act similarly. *M. psilosis* and the two related fungi contain endotoxins, which, however, are not hemolytic and are not specifically antigenic when tested intradermally on immunized rabbits, cases of sprue and human controls. A filtrable nonhemolytic exotoxin can also be demonstrated in each of the three fungi.

These observations do not support the theory that *M. psilosis* is an etiologic factor in tropical sprue.

AUTHORS' SUMMARY

THE PREPARATION OF ANTIGENIC SPECIFIC SUBSTANCE FROM STAPHYLOCOCCUS PYOGENES AUREUS H. B. DAY, Brit. J. Exper. Path. **9** 198, 1928

Experiments are described in detail which prove that the specific substance from staphylococci is liberated in an active antigenic state. Complete loss of activity follows unless the free specific antigen is protected from the action of living cocci and their enzymes. This destructive effect is not immediate, so that it is possible to obtain active specific substance, from staphylococci undergoing rapid autolysis, by methods which ensure prompt sterilization and cessation of further enzyme cleavage. The best results are obtained by extracting staphylococci at a temperature which destroys enzymes.

AUTHOR'S SUMMARY

IMMUNITY AND ALLERGY IN THE PATHOGENESIS OF TUBERCULOSIS ALLEN K KRAUSE, *Tubercle* 10 22, 1928

The author discusses briefly in this article immunity and allergy in tuberculosis, and points out the manner in which allergy creates symptomatology as well as the fact that it leads to immune effects. In every established tuberculous infection we may think of every increase of intrafocal tubercle bacilli, or every conveyance of bacilli beyond their focal bounds as met by allergic reactions. In the vast majority of countless instances the number of bacilli concerned are too small to lead to appreciable or sensible effects. Their fixation, immobilization and perhaps partial or complete destruction are accomplished. This end-result is conceived of as immunity. Large numbers of bacilli originate more severe to florid reactions, when illness, pathogenesis, now features clinically the "effort" to halt the progression of bacilli (infection), that is, to accomplish again what will appear as immunity, if only the patient recovers from the illness. It is further pointed out that fulminating tuberculosis is the expression of intense allergeo-immune action, and that immunity and allergy are competent under average conditions.

H J CORPER

RESEARCHES ON THE RESISTANCE OF DIPHTHERIA AND DYSENTERY TOXINS TO DIFFERENT HYDROGEN ION CONCENTRATIONS C IONESCO-MIHAIESTI and A DAMBOVICEANU, *Arch Roumaines de Path Exper et de Microbiol* 1 115, 1928

The destruction of these toxins by acid and alkaline solutions was not immediate. Inoculations into guinea-pigs thirty minutes after preparation of the dilutions showed the limits between which diphtheria toxin maintained its activity to be  $p_H$  4.7 to 4.9 and 9.6 to 10.01. After twenty-four hours, the extreme limits of toxicity were 5.7 to 5.9 and 9 to 9.4. With dysentery toxin inoculated into rabbits, thirty minutes after preparation, toxicity was demonstrated between the limits of  $p_H$  2.07 to 2.15 and 11.0. After twenty-four hours, a  $p_H$  of 2.5 to 3 destroyed the toxin completely, while  $p_H$  3 to 3.5 caused attenuation. The limit on the alkaline side could not be determined. It appears that diphtheria toxin is more sensitive to the action of acids and alkalis than is dysentery toxin.

INTERFEROMETRIC AND CHEMICAL DEMONSTRATION OF ABDERHALDEN'S SERUM-FERMENTS E KUSTER and K KOULEN, *Fermentforsch* 9 265, 1928

The interferometric method has been suggested for the quantitative determination of Abderhalden's ferments in serum, but the results obtained so far has been irregular. The authors investigated the hypothesis that there are at times ferments in serum which, through decomposition or hydrolytic splitting of added organic substrate, cause an increase in concentration which can be measured with the interferometer.

In sterile serum kept at 37 degrees, an increase in amino-acid nitrogen was demonstrated, but a certain increase in the interferometric value could not be found. The addition of kaolin to the serum did not increase the natural autolysis, even after forty hours incubation. Dialysis of serum against distilled water led to a stronger ninhydrin reaction in the dialysate than dialysis against physiologic solution of sodium chloride, but the increase was no greater than that occurring in serum kept in the incubator for an equal length of time. The autolysis could be attributed either to ferment activity or to a physicochemical process.

Fresh and inactivated serums from pregnant and nonpregnant persons were mixed with placental substance, and the interferometric increase and ninhydrin reactions determined. No constant differences between the serums were found. Since decomposition in active and inactivated serums was frequently the same, the splitting appeared to be to a great extent independent of ferment activity. Further experiments supported the hypothesis of Pregl, that increase in concentration of the mixtures is partly due to swelling of the added organic powder in the serum, with absorption of water. This effect could be avoided by allowing the swelling

to take place previously, according to a method described by Pregl. Even after elimination of this source of error, the action of placental substance on serum revealed a frequent increase in nonprotein nitrogen without relation to changes in the interferometric index. Several serums with marked increase in nitrogen showed but little change in the interferometric value, and vice versa. No constant relationship could be demonstrated between interferometric index and clinical diagnosis, and no clinically significant results were obtained with this method.

The authors found further that organic substrates in alkaline buffer solutions and in serum effect a shift in  $p_H$  toward the acid side. Under these conditions, a part of the substrate went into solution, that is, a purely physical process took place.

B. R. LOVETT

#### INHERITANCE OF BLOOD GROUPS K. H. BAUER, *Klin Wchnschr* 7 1588, 1928

Bauer presents a theory of blood group inheritance, based on the coupling and the exchange of germinal factors. The term coupling of factors refers to the presence of different factors in the same chromosome. The term exchange of factors refers to the breaking up of this coupling and the separation of factors that have heretofore always been transmitted together. This occurs when there is synapsis of homologous chromosomes, with subsequent separation, in which fragments of one became included in the other. This theory explains the O and AB children of O  $\times$  AB marriages, which Bernstein's theory totally fails to explain, and which Dungern and Hirschfeld's theory would lead one to expect in much greater numbers than they actually appear. In 174 O  $\times$  AB marriages, with 474 children, the latter were found to be distributed among the blood groups as follows: O, 22; A, 216; B, 204; AB, 28.

#### CHANGES OF THE BLOOD IN SYPHILIS F. KLOPSTOCK, *Klin Wchnschr* 7 1896, 1928

The changes of the blood in syphilis are caused by the invasion of the spirochetes. The peculiarity is that a lipid combination of the spirochete and not a protein substance is the antigen which stimulates immune substances.

AUTHOR'S SUMMARY

#### THE SIGNIFICANCE OF THE BLOOD GROUP AND OF PLASMODIUM SPORULATION ON THE TYPE AND INCUBATION PERIOD OF MALARIA G. HOPF, *München med Wchnschr* 75 1755, 1928

With intravenous transfer of malaria into compatible recipient, there is an incubation period of four days or less. A longer period exists with incompatible bloods. With the transfer of the quotidian type in the last half of the afebrile period, especially three or four hours before the chill, even though the bloods are incompatible there is no delay of the incubation period, but there is a tendency to the tertian type of infection. This is interpreted to mean that the injury caused by the agglutination of the red cells also affects the enclosed plasmodia.

E. F. HIRSCH

#### AUTO-ISO-AGGLUTINATION H. D. E. MILDERS, *Nederl Tijdschr v Geneesk* 72 4108, 1928

In a patient with cirrhosis of the liver a severe internal hemorrhage made blood transfusion necessary. The patient belonged to group O. A donor was found in a brother whose blood group was the same, but when, before operation, the two bloods were brought together, agglutination took place. Furthermore, the patient's serum was found to agglutinate his own blood cells. Pseudo-agglutination was thought of, but ruled out. The patient's serum was then tried out with the blood of other persons belonging to group O. Agglutination took place in every case. The examinations were repeated in a moist chamber at a tempera-

ture of 37 C Under these conditions the agglutinations no longer took place The transfusion was carried out and there were no untoward effects The patient was twice reexamined, two months and five months, respectively, after the transfusion The phenomenon of auto-agglutination was unchanged It was found in three other patients with cirrhosis of the liver, in one the blood cells were agglutinated by the ascites fluid as well as by the serum

## Tumors

INFECTIOUS MYXOMA IN RABBITS JOSEPH R HOBBS, *Am J Hyg* **8** 800, 1928

This condition, which resembles both an infectious process and a tumor growth, is apparently caused by a virus which can be recovered from exudates in the nose, eyes and infected cutaneous tissue Infection is produced by rubbing the virus material over scarified skin, or by introduction of it into the nasal passages The virus is filtrable through Berkefeld V filters, but not through Berkefeld N or Chamberland L5 or L7 filters The virus is present in the blood stream of infected animals It can be kept infective in pieces of myxomatous tissue in 50 per cent glycerin in the icebox for at least a year The virus can be destroyed by certain chemicals and by radiation The response of tissue to infection with it is peculiar to the virus and distinct from the response of tissue of the rabbit to infection with bacteria or protozoa

PEARL ZEEK

MULE SPINNERS' CANCER S A HENRY, *J Hyg* **28** 100, 1928

The largest number of cases occur after a period of contact of from thirty-five to thirty-nine years (186 per cent), though as many as sixty-three years, or possibly more, may sometimes be necessary It is not essential that the exposure to the carcinogenic agent should be continuous, and the disease may declare itself long after the patient has retired from the industry

AUTHORS' SUMMARY

TUMORS OF THE SKIN AND MAMMARY GLAND CAUSED BY PYROGENOUS PRODUCTS OF CHOLESTEROL E L KENNAWAY and BASIL SAMPSON, *J Path & Bact* **31** 609, 1928

The products obtained by heating cholesterol to about 800 C caused epithelioma of the skin in mice and a duct papilloma of the mammary gland in a rabbit

AUTHORS' SUMMARY

GIANT-CELL TUMORS OF BONE IN A FOWL S L BAKER, *J Path & Bact* **31** 657, 1928

In this article, the author describes a giant cell tumor at the upper end of the tarsometatarsus of a fowl, which seems to be indistinguishable from the giant cell tumor found in human bones

THE OXYGEN TENSION NECESSARY FOR THE MITOSIS OF CERTAIN EMBRYONIC AND NEOPLASTIC CELLS G PAYLING WRIGHT, *J Path & Bact* **31** 735, 1928

In tissue cultures, the lowest oxygen tensions at which division of cells takes place are, for myoblasts of chicken heart, about 12 mm of mercury, for cells of Jensen rat sarcoma, about 6 mm of mercury, and for cells of mouse carcinoma 2146, about 3 mm of mercury, corresponding to 1.6, 0.8 and 0.4 per cent of oxygen at atmospheric pressure

AUTHOR'S SUMMARY

CHORDOMA OF THE VERTEBRAL COLUMN WITH THREE NEW CASES D F CAPPELL, *J Path & Bact* **31** 797, 1928

Three cases of chordoma are recorded, in each of which the growth occupied an unusual site in the vertebral column, two occurring in the cervical and one

in the dorsal region. One of these presented interesting histologic features which recapitulate in a striking manner the ontogenetic and phylogenetic evolution of the notochord, a brief outline of which is given. The embryology of the notochord in the human subject has been studied, and certain aberrations of development have been observed which are in agreement with the observations of Peyron and of Linck and Warstadt.

## AUTHOR'S SUMMARY

CHORIO-ANGIOMA KARI MAYER, Arch f Gynak **134** 482, 1928

Chorio-angioma, hitherto described under various names, is not an uncommon tumor of the placenta, but nevertheless Mayer believes that a routine study of placentas might uncover more of these tumors. Thus the cause of abortions, prenatal deliveries, polyhydramnios and certain unexplainable neonatal deaths, associated with this tumor, might be cleared up. The growth consists essentially of a blood vessel tumor embedded in a connective tissue matrix. It is easily shelled out. The parenchyma consists of a growth of blood vessel endothelium with typical capillary formations. Mayer gives a detailed description of a case that came under his own observation and reviews the literature.

A J KOBAK

## Medicolegal

SUDDEN DEATH FROM JELLYFISH POISONING IN STATUS LYMPHATICUS H W WADE, Am J Trop Med **8** 233, 1928

A well developed, healthy young man, with only slight remaining evidences of leprosy, was working waist deep in the water of a mangrove swamp when he called out in distress to fellow workmen nearby that something had bitten him. He quickly collapsed, breathing with difficulty, and died within a very few minutes. Wade could not find any mark suggestive of a snake bite, or any other abnormality except purplish (livid) markings ascribable only to contact with a large, long tentacled jellyfish. The head was livid. The lungs were distended and did not collapse, they contained much frothy serous material that had escaped from the alveolar capillaries. The right side of the heart was full, and the blood was fluid and dark. The viscera were congested, especially the kidneys, which showed parenchymatous injury and albuminous material in the glomerular capsules. The fatal outcome was too sudden to be ascribed to the poisoning alone. Definite evidence of status lymphaticus was found, and it is probably because of the peculiar instability known to exist in this condition that the unquestionably severe shock of the jelly-fish sting induced sudden death.

THE FATE OF MORPHINE INJECTED INTO THE ANIMAL BODY Y TLRUCHI and S KAI, J Pharmacol & Exper Therap **131** 177, 1927

Morphine is not easily destroyed in the animal body. In an examination of the entire body of rabbits into which it was injected from three to sixteen hours before, almost the entire amount was recovered. In suspensions of liver, lungs and kidneys of rabbits outside the body, morphine was not destroyed in four hours at 38 C. Protection against the poison is aided by its storage (about 30 per cent) in muscles and by excretion. Excretion from the blood into the stomach occurs before excretion into the urine, but after some hours they proceed apace. Taken through the liver from the stomach and bowel, the drug may follow the same route again.

In chronic poisoning, the amount stored in muscles is greater, and both excretion and the ability to destroy morphine are augmented. In chronic morphine poisoning, the amount in the blood is larger than in acute poisoning. It is present in plasma and blood cells in equal amounts. In acute poisoning, as much as 90 per cent may be recovered, but in chronic experimental poisoning in rabbits only about one sixth of the amount injected.

E R LE COUNT

OCCUPATIONAL DISORDERS FROM PNEUMATIC TOOLS E LONG and F NAVILLE,  
J de med de Lyon 8 577, 1927

Observations are reported of the curious symptoms that are produced by the rapid vibrations transmitted to the bodies of laborers from pneumatic tools, and by the constant cold to the hands or other parts exposed to the blast of compressed air. Five cases are described with nothing of moment not covered by a report from the Bureau of Labor at Washington in 1918, based on evidences of this occupational disease in 68 of 100 stonecutters examined. The present report contains an especially interesting discussion of the legal interpretations of what constitutes an accident in different countries, and the need of greater uniformity. One of the five patients was refused award for damages at three separate hearings, notwithstanding the fact that his symptoms persisted for three years after he changed his occupation. Some patients have vasomotor disorders which simulate Raynaud's disease.

E R LE COUNT

UNUSUAL WOUNDS OF THE URINARY BLADDER HORTOLOMEI, J d'urol 24 286,  
1927

Abrupt, uncontrollable cessation of urination leading to efforts to urinate from twenty to twenty-five times a day, urination being easier when the patient was sitting or lying down, led to the discovery of an unbruised shrapnel ball free in the bladder and without incrustations. The wound was received six years previously. The symptoms began two years after the injury. In another patient, the wounds of entrance and exit made with a revolver bullet healed without operative intervention. After the acute symptoms had subsided, the wounds were seen cystoscopically.

E R LE COUNT

DISTURBANCES OF LIVER METABOLISM IN CHRONIC ALCOHOLISM P BUCHLER,  
Arch f Psychiat 81 280, 1927

Many of the minor late effects of the poisonous action of alcoholic beverages are not outspoken disease requiring prompt medical attention. They are vague symptoms, not present all the time, and in the beginning only one or two are evident. They take the form of loss of attention, will power and initiative, inability to concentrate, lowered morale, illusion, and hypnagogic hallucinations. They are commonly referred to under the general designation, chronic alcoholism. A state of prepsychosis or of subdelirium is attained when such symptoms of impaired mentality are numerous and pronounced.

There are two views of the pathogenesis of this chronic alcoholism and of the more clinically definite delirium, psychoses and epilepsy which follow poisoning with alcohol. One explanation is that they are all brought about by action of the alcohol on the liver and hepatotoxins accruing from this action. The other attributes them to generalized disturbance of metabolism and vitiated ferment actions caused by increased oxidation of phosphatides and the resulting ketoacidosis.

Reports of a number of investigations have been made by Buchler. One was a study of the blood in 105 patients, including observations made up to 1925. The results of that examination are included with this report of changes in the blood of forty-five more patients, altogether 150. The evidence of damage, least in persons with the vague symptoms so conveniently disposed of as chronic alcoholism, steadily mounts as disease becomes more clearly evident clinically and is most marked with delirium and severe psychoses.

Fat splitting properties of the blood, said to be due to lipases formed only when the liver is diseased and not inhibited by quinine as are the lipases normally present, were found well developed in persons with the fewest symptoms, 66.7 per cent as compared with the 100 per cent associated with psychoses and delirium. In the poorly defined chronic alcoholism, coagulation of the blood was slower, 20.9 per cent, with psychosis, 31.2 per cent, with delirium, 76.2 per cent.

A third and valuable indication of pathologic disturbances was urobilinogenuria. This condition, reduced to a percentage basis and sought in 140 patients, was 39.3 per cent in simple chronic alcoholism, 48.7 per cent with psychosis and 81.2 per cent when delirium was present.

Other disorders, such as diminished tolerance for galactose, a high serum bilirubin, toxic amines in the blood and hypercholesterinemia, were all more pronounced as the results of alcohol poisoning became more serious. The bilirubin content was only from 1 to 2 mg per hundred cubic centimeters of blood, Buchler explained this by the lower content of alcohol in the Hungarian wine which was responsible for the conditions he studied. When the beverage was largely brandy, other observers found from 4 to 6 mg of bilirubin. The indications of grave pathologic metabolism gradually disappear with recovery from delirium, but in the alcoholic psychoses they are more permanent. A congenital abiotrophy of the central nervous system or an abnormal intolerance for alcohol are suggested for the few changes of the blood in 11 per cent of the patients with delirium.

E R LE COUNT

ABORTION WOUNDS WINTER, *Deutsche med Wchnschr* 53 1931 and 1976, 1927

This is a long account of how wounds of the uterus are made by physicians, of the more and less dangerous instruments, of how such wounds may be avoided and of safely performed abortions. The article is mainly clinical. But slight reference is made to the injuries inflicted by midwives and worse bunglers, such as are encountered in mediocolegal work. There are interesting references to the literature—to the reports of 357 perforations in the practice of ninety-five physicians of Westphalia and the lower Rhine region, to 2.9 per cent of 443 perforations being made with the finger, to 134 cases during thirteen years—reported by one observer, etc. The small curet is considered the most dangerous tool. Nonpregnant uteri are less often, and those of women many times pregnant most easily, perforated. Winter believes that perforations are made accidentally by physicians more often than in the practice of abortion. Questions of malpractice and of criminal guilt are more common than ever before, likewise, the endeavor to secure monetary indemnification rather than legal punishment.

E R LE COUNT

CHRONIC TRAUMATIC EDEMA RAESCHKE, *Klin Wchnschr* 6 1763, 1927

Chronic traumatic edema occurs at all ages, usually involves extremities, may last a few hours or throughout life and has a varying firmness. Lymph accumulates in the tissues, and there may be marked disease of the blood vessels, especially capillaries. In the case reported, the right arm was affected following a crushing injury. At one operation for the edema, the sympathetic nerves were dissected from the brachial artery, at another, all the fascia of the arm and hand down to the finger joints was removed. Finally, the arm was amputated. After this, bad news caused swelling of the stump, but the edema disappeared when the alarm proved groundless. It was then learned that the patient, a man, desired the amputation to obtain indemnification and start a small business.

E R LE COUNT

MYOSITIS OSSIFICANS TRAUMATICA M STRAUSS, *Klin Wchnschr* 6 699, 1927

Four months after the dislocation of one hip, roentgen examination disclosed a mass of spongy bone, extending from the great trochanter of the femur on that side up to the innominate bone. It was in the muscles and unconnected with adjacent bone. A large mass of metaplastic bone caused by trauma, also located about one innominate bone, was described by Eben J Carey (*Tr Chicago Path Soc* 11 356, 1923). This case was especially interesting because microscopically a change to sarcoma had occurred in a few places.

E R LE COUNT



POLYNEURITIS FOLLOWING ACUTE THALLIUM POISONING R GREVING and  
O GAGEL, *Klin Wchnschr* 7 1323, 1928

A widow, aged 30, attempted to commit suicide by eating, with bread, one-half tube of "Celiopaste," containing a preparation of thallium, used as rat poison. Two days later, she experienced anorexia and cramping sensations in the chest and toes. Ten days later, the left patellar and achilles reflexes were lost, the left ankle and calf were hyperesthetic and the leg, when lifted, felt lifeless. Excruciating pains in the extremities in five attacks lasting from a month to a week were noted during the patient's five months' stay in the hospital. There was a loss of scalp hair on the twelfth day after poisoning and at irregular intervals short attacks of myocarditis. The menses stopped for four months. The noteworthy features of the examinations of the blood were white cells, 5,500, eosinophils, from 6 to 11 per cent, and lymphocytes, from 28 to 30. Gastric acidity was found to be free acidity, 6, and total acidity, 15. Experiments on small animals promise a polyneuritis following ingestion of a thallium compound.

GEORGE RUKSTINAT

THE INCREASING FREQUENCY OF POSTOPERATIVE PULMONARY EMBOLISM J  
OEHLER, *Munchen med Wchnschr* 74 1662, 1927

This report was made at a meeting of surgeons of Northwestern Germany in December, 1926. The discussion (*Zentralbl f Chn* 54 939, 1927) supported Oehler's contention that there has been recently a marked increase in the number of deaths from postoperative pulmonary embolism, Oehler and others believe this increase is due to the administration of various drugs intravenously. Mention is made of calcium chloride, urea and of preparations supposed to lessen the likelihood of postoperative pneumonia. Some of these contain calcium and, presumably, promote coagulation of the blood. But the increase in the number of deaths from these causes is not entirely postoperative, for Fahr of Hamburg reported an increase from the intravenous administration of remedies for such nonsurgical conditions as apoplexy and diseases of the heart and blood vessels. During the years 1915 to 1923, Fahr found twenty-four deaths from pulmonary embolism in 1,200 postmortem examinations, with a percentage of from 1 to 4.2 for each year (*Klin Wchnschr* 6 2179, 1927). In the period from 1925 to 1927, however, he encountered 146 in 1,800 postmortem examinations, and of these ninety-five were unconnected with operations. In the discussion of Oehler's paper, statements were made of a falling off in the number of deaths when intravenous medication was discontinued.

E R LE COUNT

DROWNING FROM WATER IN THE EARS GUTTICH, *Munchen med Wchnschr*  
74 1919, 1927

Experiments were made with the vestibular caloric reaction in guinea-pigs and in swimmers bathing in an inside pool. With the head out of the water, cold water in one ear causes swimming in a circle, especially when vision is obstructed. With the head under water, a somerset-like tumbling may occur, the head pitching forward. Such reactions may occur with the tympanum intact, but with perforated drum membranes they take place more readily and more promptly. There is little likelihood that the nystagmus will occur while a person is swimming in still water with the head out. The time under water in diving is usually too short for disorientation to become dangerous except when the ear drums are perforated. With animals on land, a corkscrew-like rolling has been produced.

E R LE COUNT

THE MEDICOLEGAL SIGNIFICANCES OF THE CORPUS LUTEUM OF PREGNANCY  
H KATZ, *Munchen med Wchnschr* 75 1291, 1928

A divorcee, aged 22, having had illicit relations, noticed that the menstrual period of June was shorter than that of May, the July period was absent

Because of pain in the lower part of the abdomen, she sought medical attention at a hospital. A cyst of the right ovary was found on examination, and operative removal was advised. The enlargement of the uterus was about that of the second month of pregnancy. The right adnexa, including the ovary with a cyst the size of a pigeon's egg and a well preserved corpus luteum, were removed on July 19. After nine days, the woman left the hospital and for five days thereafter had pain and uterine hemorrhage. Believing herself pregnant and wishing to have an abortion she went to Dr. X, who repeatedly had come to the notice of the authorities because of the suspicion that he had performed abortions. She reported to him that she was pregnant, and he, without further inquiry, made intra-uterine manipulations. When arraigned in court, he excused his uterine intervention on the basis that he believed a hydatid mole was present. This conclusion was reached because he thought the uterus was too small for a nine to ten weeks' pregnancy, as the cervical canal was patent for a little finger, after little dilation, he had inserted, without trouble, a large curet and removed from the cavum only small fragments of brown tissue.

The expert testimony brought out that destruction or removal of the corpus luteum of pregnancy during the early months of pregnancy is likely to result in abortion, and lead to the acceptance of Dr. X's statements and his release by the court.

E. F. HIRSCH

SYMMETRICAL GANGRENE OF THE FEET FROM PHOSPHORUS POISONING. H. ROSSIER, *Schweiz med Wchnschr* 57 890, 1927

As a result of melancholy, a young woman took 3.5 Gm of rat poison, except for a little abdominal distress and vomiting, she was able to perform her work as usual for four days. The abdominal pain then increased, and a small degree of icterus was noticed. On the fifth day, 1 per cent of sugar was found in the urine, that night, pain was noted in the feet which were hot. Pulsation in the arteries of the lower extremities was normal. The next day, the great toes were livid and cold, and gangrene subsequently spread to other toes and the adjacent plantar parts. Death occurred on the tenth day. Phosphorus was not found chemically in material obtained from the body after death. Comment is made on the failure to examine the vomitus and stools before death, and the arteries of the lower extremities at the time of the postmortem examination. There was no hypoglycemia, and the glycosuria followed lowering of the renal threshold for sugar retention. An increased ease of lysis of the patient's red cells in test tubes was also noticed. Icterus became marked, death in coma resulted.

E. R. LE COUNT

PSYCHIC DISTURBANCES AFTER ATTEMPTED SUICIDAL HANGING. F. SALINGER and H. JACOBSON, *Ztschr f d ges Neurol u Psychiat* 110 372, 1927

Different opinions have been advanced regarding the peculiar symptoms which follow strangulation by hanging in persons who have been found in time, cut down and brought back to life. Before consciousness returns, convulsions usually occur, and in many persons these have been followed by a transitory mania. These symptoms have been accepted as results of the cerebral anemia. The controversy has been mainly with the retrograde amnesia, emotional instability and symptoms of psychosis which follow return to consciousness and persist for days. By some, these have been explained as hysteria and as unconnected with changes in the brain due to strangulation. Others have maintained that all the symptoms originate in organic cerebral lesions.

In reporting a case with symptoms lasting three days after the return of consciousness, the authors include an excellent review of the reports of fifteen others, together with the explanations offered. The presentation is conservative, but tends toward explaining everything by organic changes. It seems safe to predict from the outcome of studies made of the brains of persons with similar symptoms from carbon monoxide poisoning, that if the opportunity is presented

to study the brains of persons almost strangled to death, there will be little difficulty in accounting for all the symptoms. Now and then, with carbon monoxide poisoning the approach to death is close and recovery protracted, and a wide range of manifestations of altered mentality and even dementia result. In both conditions, there is deprivation of oxygen and probably poisonous action of substances normally rendered harmless by the usual supply of properly oxygenated blood, or removed by the usual circulation of healthy blood.

E R LE COUNT

PARALYSIS AGITANS AND TRAUMA E HENSSGE, *Ztschr f d ges Neurol u Psychiat* **110** 796, 1927

Paralysis agitans was first noted three months after a fall in one patient and six months after in a second. One was 42 years old and the other 52, and they were not prematurely senile. The tremors began on the side injured, and accounts of the injuries were thoroughly reliable. Others have commented on the high ratio of trauma with this uncommon disease. The back and forth play of nervous impulses between muscles and the central nervous system, the unusual demands on muscles to maintain equilibrium during falls and minimize injury and the terminal character of the arterioles in basal ganglions and other parts of the brain involved are given as reasons for a causal relationship.

E R LE COUNT

SPONTANEOUS RUPTURE OF THE AORTA DURING LABOR P BOHNEN, *Zentralbl f Gynak* **51** 2398, 1927

Death in labor, at the ninth month, from a spontaneous transverse rupture of the aorta, 2 cm distal to the aortic leaflets, is reported. Marked arteriosclerosis and loss of renal parenchyma from chronic disease was noted. According to Bohnen, there are only four similar reports in literature of rupture during labor. According to different authorities, the blood pressure is increased from 60 to 100 mm of mercury during labor pains.

E R LE COUNT

CORROSION OF THE URINARY BLADDER, DILATED URETERS AND RENAL PELVES FOLLOWING ATTEMPTED ABORTION R ANDLER, *Zentralbl f Gynak* **51**. 2921, 1927

Severe corrosion of the lining of the urinary bladder occasionally results from the injection of solutions through the urethra instead of into the uterus in attempts to produce abortion. Chlorinated lime, soap with pepper and iodine have been used. In Andler's patient, about 20 cc of a concentrated solution of albumin acetate was tried. The acute symptoms of corrosion lasted many months, and when they improved pain in both kidneys was noted, with tenderness and enlargement of the right kidney. Cystoscopic examination showed that the ureteral mouths were greatly enlarged and funnel-shaped, and roentgen examination after the injection of collargol disclosed marked dilatation of the ureters and renal pelvis.

Mention is made of the reports of five other cases of corrosion of the bladder from efforts to cause abortion, with only one abortion actually produced, and of one corrosion as the result of a fear of gonorrhea. With the corrosion of the vesical lining, it is believed that a paralysis of the muscles in the walls of the ureters at their lower ends occurs, and such systolic force as the bladder exerts dilates the ureteral orifices. After this, the dilatation upward of the urinary passages takes place.

E R LE COUNT

## Technical

THE EFFECT OF EXTERNAL TEMPERATURE ON THE SEDIMENTATION RATE OF THE RED BLOOD CORPUSCLES MURRAY B GORDAN and DAVID J COHN, *Am J M Sc* **176** 211, 1928

External temperature was found to exert an influence on the sedimentation rate of the red blood cells. Higher temperatures accelerate the rate and lower temperatures diminish it, therefore, the sedimentation test should be performed under controlled temperature conditions

PEARL ZEEK

THE PHENOLTETRACHLOROPHTHALEIN TEST OF LIVER FUNCTION IN THE LATE TOXEMIAS OF PREGNANCY SAUL BERMAN, *Am J Obst & Gynec* **16** 410, 1928

Berman concedes that this test has no practical value in late toxemias. One hundred and eighteen cases were investigated. In twenty convulsions occurred and in ten of these cases retention of the dye. Of the six patients who died only three retained any of the dye. Nephritic and pre-eclamptic toxemias could not be differentiated by this test of dye retention. The majority of patients with chronic nephritis did not show retention.

A J KOBAK

THE VALUE OF THE DIAZO TEST OF BLOOD S M RABSON and L JACOBS, *Arch Int Med* **42** 386, 1928

The diazo test was positive in 7 of 415 consecutive specimens of blood from a hospital ward, and in 40 specimens from patients with severe cases of nephritis. The test was positive in blood with a low creatinine content and negative with creatinine values of 3 mg per hundred cubic centimeters of blood or more. Uremia did not always give a positive test, even in the presence of coma. In one case in which there was obstruction of the kidney, the positive reaction became negative on relief from the obstruction.

HAMILTON R FISHBACK

THE DEXTROSE-TOLERANCE TEST ITS USE IN THE DETERMINATION OF THE SEVERITY OF DIABETES MELLITUS M WISHNORSKY, *Arch Int Med* **42** 443, 1928

The amount of glycosuria during the dextrose tolerance test does not indicate the severity of the diabetes. The true criterion is found in the character of the blood sugar curve.

HAMILTON R FISHBACK

A NEW CLINICAL TEST FOR TISSUE THIRST W A THOMAS and E ANDREWS, *Arch Int Med* **42** 776, 1928

On dialyzing normal blood serums against hundredth-normal hydrochloric acid, the absorbing power varied from 1 to 9 per cent. Serums from patients with nephritis, uremia and edema of cardiac origin gave hydrophilic values of from 15 to 50 per cent. This value may be due to some foreign protein in the blood or to some change in the colloid dispersion of the normal proteins of the blood.

HAMILTON R FISHBACK

DETERMINATION OF SUGAR IN CEREBROSPINAL FLUID BY BENEDICT'S COPPER METHOD ROGER S HUBBARD, *Clifton M Bull* **14** 123, 1928

There are rather marked differences between the spinal fluid sugar when determined by methods as different from each other as are Benedict's copper and picric acid methods, but the differences are not as great as are those found in blood. The copper methods of Benedict and Folin and Wu give almost identical values when applied to spinal fluid, although there are marked differences in the results

when the same methods are applied to blood. It seems probable, therefore, that there are nondextrose-reducing substances in blood, which either do not enter the spinal canal or which pass into the fluid only in relatively small amounts. The range of reducing compounds in the spinal fluid is probably almost exactly the same as is that in blood, namely, 30 mg per hundred cubic centimeters, but the amounts are decidedly smaller. This difference for Benedict's copper method seems probably to be about 20 mg per hundred cubic centimeters. The actual range of Benedict's copper reduction method obtained under fasting conditions is probably from about 50 to approximately 80 mg per hundred cubic centimeters, although a conservative interpretation should be placed on results slightly higher or lower than these limits. Interpretation of high values should almost certainly be made only in connection with blood determinations carried out on samples obtained at the time when the specimens of spinal fluid are taken. Plasma studies should form a more satisfactory basis for such comparisons than do those on whole blood, because there are reducing compounds in the cells which apparently do not penetrate into the plasma, just as there are similar compounds which do not enter the spinal canal from the blood.

AUTHOR'S SUMMARY

**SINGLE CELL TECHNIC. A PRESENTATION OF THE PIPETTE METHOD AS A ROUTINE LABORATORY PROCEDURE.** A. H. GEE and G. A. HUNT, *J. Bact.* **16** 327, 1928.

The pipet method of procuring single cell bacterial cultures is described in a form which can be applied as a routine procedure requiring a minimum of special equipment. Attention is directed to the steps in the technic which are essential for success, and certain refinements are offered. Accessory equipment recently devised by various workers and of service in work with organisms that are difficult to cultivate is reviewed briefly.

AUTHORS' SUMMARY

**A GASOMETRIC METHOD FOR DETERMINATION OF REDUCING SUGARS, AND ITS APPLICATION TO ANALYSIS OF BLOOD AND URINE.** D. D. VAN SLYKE and J. A. HAWKINS, *J. Biol. Chem.* **79** 739, 1928.

"A gasometric method is described for determining reducing sugars. The latter are permitted to react with ferricyanide, of which an amount proportional to the sugar is reduced to ferrocyanide. The decrease in ferricyanide caused by the sugar is measured by the decrease in the pressure of  $N_2$  gas observed when the ferrocyanide liberates  $N_2$  from hydrazine in the Van Slyke-Neill manometric apparatus. Applications to rapid determination of sugar in blood and urine are described."

AUTHORS' SUMMARY

**MEMBRANES FOR ULTRAFILTRATION, OF GRADUATED FINENESS DOWN TO MOLECULAR SIEVES.** J. W. MCBAIN, and S. S. KISTLER, *J. General Physiol.* **12** 187, 1928.

The writers recommend the use of cellophane for ultrafiltration, and give two methods for decreasing the size of its pores until it becomes a fine molecular sieve. They emphasize the fact that ultrafiltration is a distinct process, bearing little relation to diffusion, dialysis, osmosis, electro-osmosis or thermodynamics.

H. E. EGGERS

**METHOD OF STAINING FLAGELLA.** EMIL WEISS, *J. Infect. Dis.* **43** 228, 1928.

A new method of staining flagella includes the treatment of young cultures with acetic acid (sufficient to make 5 per cent). A drop of this suspension on the slide is allowed to dry untouched, and staining is first produced with a basic dye and then with an acid dye. Useful contrastive stains were saturated gentian or crystal violet and acid green, Löffler's methylene blue (methylthionine

chloride, U S P) or aqueous thionine blue and acid fuchsin, brilliant green and acid fuchsin or acid violet and carbol fuchsin and acid green. This method is also useful for the demonstration of degenerated or phagocytosed bacteria.

#### AUTHOR'S SUMMARY

THE HINTON GLYCEROL-CHOLLSTEROL TEST FOR SYPHILIS. AUSTIN W. CHEEVER and RUSSELL L. SPLAINE, New England J. Med. **199** 967, 1928

A detailed description of this test as recently modified will be published soon. The technic used by Cheever and Splaine is described by Hinton (*Boston M. & S. J.* **196** 993, 1927). The results obtained in 1,610 cases are discussed. In 260 cases in which discrepant reactions occurred, the Hinton test gave the largest number of positive results in known syphilitic cases and as few false positive reactions in the nonsyphilitic cases as any of the other methods used for comparison, such as the Wassermann test, the Kahn test and the slide test of Kline and Young. The results are interpreted as showing that the Hinton test is a more sensitive test for syphilis than the others. The authors also conclude from their data that a negative reaction to the Hinton test is a safer criterion of cure than a negative Wassermann reaction of the test blood serum.

BLOOD GROUPS AND PATERNITY. G. HASELHORST, *Klin. Wchnschr.* **7** 1816, 1928

The blood groups O, A, B and AB in 1,000 men were, respectively, 41.10, 41.80, 13.10 and 3.00 per cent; in 3,000 women, they were 39.33, 43.70, 12.73 and 4.23 per cent. Among 750 determinations of mother and child, 400 of which included also the father, there were only two exceptions to the inheritance rules of von Dungern and Hirsfeld and none to the general scheme of Bernstein. A plausible explanation was found for one of these exceptions, but not for the other.

E. F. HIRSCH

# Society Transactions

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## NEW YORK PATHOLOGICAL SOCIETY

*Regular Monthly Meeting, Nov 8, 1928*

HARRISON S. MARTLAND, *President, in the Chair*

DEMONSTRATIONS OF RARE UTERINE TUMORS MYOMA WITH FATTY CHANGE, LIPOMYOMA, FIBROLIPOSARCOMA, MYXOMYOSARCOMA ALFRED PLAUT

*Myoma with Fatty Change*—This specimen, the soft body of the uterus of a married woman, aged 47, chiefly consisted of a ball-shaped myoma, 12 cm in diameter. A sausage-shaped continuation of the myoma distended the cervical canal and appeared like a polyp in the external os. The uterine cavity was stretched posteriorly over the tumor. The cut surface was as usual, half gray and half yellow, with a hue similar to that seen in xanthomatous or pseudoxanthomatous foci. The outer and lower parts were more yellow, the inner and upper portions were gray. The structure, however, was the same over the whole cut surface, it was entirely that of a myoma. That was seen much more clearly in the fixed specimen than appeared immediately after operation. Microscopically, most of the muscle cells in the yellow areas were filled with fat droplets, they assumed a brilliant red color with the sudan IV stain. Large and small droplets more or less completely filled the space between the nucleus and the outline of the muscle cell. Pigment was not found. In spite of the frequency of secondary changes in myoma uteri, such fatty infiltration is rather rare.

*Lipomyoma*—The specimen was a myoma shaped fairly like a ball, 5 cm in diameter, which was shelled out from the lateral wall of the uterus of a woman, aged 58. The surface and cut surface exhibited small spots obviously of fat tissue. They occupied about one tenth of the cut surface. The myoma tissue was pale gray and firm. The color of the fat tissue was distinctly different from that of the fatty spots in the first case. Microscopically, fat tissue and myoma tissue were intimately mixed. All the fat cells were large, lipoblasts could not be found. The myoma was partly hyalinized. Fat droplets were not seen within the muscle cells. Myometrium was not available for microscopic examination. Such tumors are extremely rare. In the descriptions of the equally rare lipomas of the uterus, the presence of occasional muscle fibers is mentioned. Perhaps such a lipoma represents a later stage of a tumor such as this, with the fat tissue occupying more and more of the original myoma. Among the theories brought forward as to the origin of the fat tissue, the assumption of undifferentiated cells seems the least improbable. Such cells must be capable of differentiating themselves into muscle cells as well as into fat cells. By calling the tumor lipomyoma, one states only that both kinds of tissue are present, without assuming to describe its histogenesis. One is not even certain that a true blastomatous process lies behind this fat tissue. One investigator has compared the process with the development of fat in dystrophia musculorum progressive (Bruenings), and one might, for comparison, think of the adipositas cordis or the fat often found in the obliterated appendix vermiformis.

*Fibroliposarcoma of Uterus*—At the age of 55, eight years after the menopause, the patient noticed an abdominal swelling. The specimen, as found at operation, was nearly mathematically ball-shaped with a diameter of 12 cm. The uterine cavity was extremely narrow, almost obliterated. Typical yellow adipose tissue occupied most of the cut surface, the remainder, about one third, consisted of pale pink and gray masses resembling connective tissue. The tissues encroached on each other and mixed. The surrounding myometrium had an average thick-

ness of 8 mm. The outlines of the tumor were distinct, although parts of it (fatty ones) reached into the myometrium. Under the microscope, cellular, partly undifferentiated connective tissue was observed with many round cells of large and medium size. The typical round spaces of the fat cells were irregularly distributed through it. In one ovary, a dermoid cyst was present.

*Myxomyosarcoma*—A married woman, aged 43, noticed an abdominal swelling. This tumor removed three weeks later from the posterior wall of the uterus had a diameter of 12 cm. It was soft and roughly ball-shaped. The cut surface revealed none of the fascicular or globular structures seen in myoma uteri. It was irregularly yellowish gray, and interrupted by many, more or less circumscribed spaces, filled with fluid. This fluid was edema-like in the upper half, while in the lower half it was cloudy and partly bloody. The solid parts were homogeneously glistening. A line of cleavage between tumor and myometrium was easily established. The microscopic picture was that of a spindle cell tumor with wide variation in size, shape, staining qualities, etc. A true myoma-like picture could be found, but an origin from muscle tissue was probable, nevertheless. The homogeneous material separating groups of tumor cells or even single cells gave a positive reaction with mucicarmine, but only when a strong solution was used. Only exceedingly little metachromasia was obtained with polychrome methylene blue. The name given this tumor is meant to indicate the highly probable origin from myoma, the malignant character of the growth and the histochemic nature of the mucin-like material. The tumor has nothing in common with myoma.

An attempt will be made to examine the patients.

#### DISCUSSION

NICHOLAS ALTER: What criteria did you have for calling the specimen sarcoma?

ALFRED PLAUT: The irregularity of the whole picture. These were all specimens calling for operative intervention. All the women are now in good health several months after operation for myoma uteri.

#### A CASE OF SUBAORTIC STENOSIS C. E. DE LA CHAPELLE

Subaortic stenosis (also known as subvalvular stenosis) is rare. In view of this and because of several unusual features, it seemed of sufficient interest to report the following case, which came to necropsy in the Bellevue Hospital mortuary (service of Chief Medical Examiner Dr. Charles Norris, to whom I am indebted for the privilege of presenting the specimen).

A. G., an obese white man, aged 55, was found dead at his home. The previous history was incomplete, the only important fact was that he had been a well-known lightweight prizefighter some twenty to thirty years prior to his death.

The heart was enlarged and weighed 490 Gm. The valves were normal, save for the aortic valve. One centimeter below the aortic cusps, and on a level with the junction of the membranous and muscular portions of the interventricular septum, there was a ridge with a well defined edge. Above, it was continuous with the endocardium of the base of the left ventricle. In this area there was a shelflike formation that blended into the undefended space. At its extremities, where it became shallow, it was continuous with the base of the aortic leaflet of the mitral valve. When the specimen was closed, the conus portion of the left ventricle was transformed into a more or less narrow canal. The circumference of the orifice formed by the anomaly was 6 cm., 2.5 cm. of which was formed by the base of the aortic leaflet of the mitral valve.

The aortic cusps were markedly but uniformly sclerosed and rigid. They were adherent at the commissures for several millimeters. A pearly plaque, characteristic of the gross lesion of syphilitic aortitis, involved the commissure between the right anterior and left anterior cusps. There were several other smooth pearly plaques scattered about the first part of the aorta. The orifices of the coronary arteries were patent. The vessels themselves were moderately sclerosed.



Microscopic examination of the aorta and an aortic cusp revealed the presence of a syphilitic process. The anomalous ridge presented an external layer of what apparently represented hyperplastic and hyalinized endothelial cells derived from the endocardium. The greater part of the anomaly, however, was made up of cells that appeared to be muscle fibers. Some were degenerate, but most of them have undergone hyalinization.

The specimen presented displayed a congenital malformation. The unusual features of this case were the age of the patient, 55 years, and the previous occupation, prizefighting. During his active fighting career, the aortic valves probably were still normal, and although the subaortic stenosis was present at that time, the function of the heart apparently was not impaired much, if any. The aortic valves probably became involved by the syphilitic process at a later period. The lesion in these valves was another unusual feature of the case, since it presented a stenosis rather than the usual insufficiency of the valves due to retraction and widening of the commissures as is so typical of syphilis. The specimen therefore really presented a "double aortic stenosis," the valvular stenosis being an acquired lesion, and the subvalvular stenosis, a congenital one.

(The gross specimen was exhibited, as well as lantern slides of the gross specimen and of sections of the aorta, aortic cusp, interventricular septum and the anomalous stenosis.)

#### DISCUSSION

E. LIBMAN. I have not made a study of this subject, but there are certain points that I would like to make concerning this presentation. This subaortic stenosis is particularly interesting because, as you see from the picture on the screen, it involves the aortic flap of the mitral valve. Occasionally, one sees a congenital membrane below the aortic valves without any stenosis. Last summer, in Amsterdam, Professor de Vries showed me two specimens presenting this condition.

In this case, we have no record of what murmurs, if any, were present. When calcification is present in the aortic flap of the mitral valve, there is apt to be present a systolic murmur, heard louder near the sternum than at the apex. The French call such murmurs *juxta-aperienne*. When there is a definite jutting out of the lime, so that a narrowing is produced, some speak of a mitro-aortic stenosis. Objection has been raised to the use of this term in this way, especially by Gallavardin. It would be of interest to hear what the literature says about the murmurs heard in cases of congenital subaortic stenosis.

The amount of sclerosis in the valve flaps is extremely interesting. Does Dr. de la Chapelle believe that the lesion of the valve is entirely syphilitic? A marked fibrosis in syphilitic aortic flaps usually appears only after they become retroverted. Then there develops a fibrosis from tension in them, and sometimes calcification. I have noted that calcification is less likely to occur in syphilitic valves than in those diseased from other causes.

I draw particular attention to this marked fibrosis because, if the stenosis is congenital, the valves ought to have been protected from strain and secondary fibrosis. There is usually no dilatation of the aorta when a stenosis is present. The question arises whether these valves may have been congenitally diseased, so that there was a congenital stenosis before the syphilitic condition occurred, or whether there was originally a congenital diffuse thickening of the flaps. If I had known before the meeting of the type of lesion that was to be presented, I would have demonstrated a picture of a mitral valve with congenital thickening (myxomatoid) of a whole flap.

HARRISON S. MARTLAND. I was under the impression that in almost all cases of subaortic stenosis the mitral valve was also involved, usually with the production of a mitral stenosis. Is that correct? The aortic cusp of the mitral valve is always thickened in these cases, is it not?

BENJAMIN SACKS. I have never had the opportunity of studying a case of subaortic stenosis. It is interesting to inquire whether this condition might not be due, at times, to an inflammatory lesion. I have recently read of a case

of subaortic stenosis associated with subacute bacterial endocarditis. In such cases, the question would be whether the subaortic stenosis preceded the endocarditis or was the result of it. Inflammatory lesions of rheumatic origin are often seen in the subaortic region on the wall of the interventricular septum, and may be of wide extent. The cases which Dr Gross and I recently studied did not show any narrowing of this region. The lesion is interesting, and one that Dr Libman has pointed out in his illustrations many times. This subaortic patch of endocarditis in rheumatic hearts was formerly regarded as a change due to tension, or one related to the aortic insufficiency. The area involved has a dry, wrinkled, corrugated appearance, and in some of the cases the lesions is similar to the auricular lesions described by Dr MacCallum and Dr von Glahn. Microscopic sections show not only diffuse inflammatory involvement, but also Aschoff bodies in the deeper layers. As far as the valvular lesion in this case is concerned, I must say that I have never seen a syphilitic valve that showed the amount of commissural fusion which this one did. This change is more frequently seen in rheumatic endocarditis, and I wish to inquire whether sections of the other valves have been made in order to determine the possible presence of a rheumatic lesion in this case, because the aortic valvular stenosis might, perhaps, be better explained on an inflammatory basis of this kind, although a syphilitic etiology is possible.

**HARRISON MARTLAND** I am sure that I have seen in syphilitic supravulvar sclerosis an extension to the aortic cusps similar to that seen in this specimen, the cusps being rubbery and markedly thickened, especially on their free edges, with little if any retraction, and hence little regurgitation.

**CLARENCE DE LA CHAPLIER** I think Dr Libman's point about the possibility of this being a diffuse congenital thickening of the aortic valve itself is good. The microscopic picture, however, was that of a syphilitic lesion. I would like to have found another congenital anomaly in this man. As you know, it is not unusual to find a second congenital anomaly in cases of congenital heart disease. He had no other congenital anomaly.

I agree with Dr Sacks as to the appearance of the aortic valves, and I believe I mentioned that this valvular lesion was contradictory to the usual condition of the valves as found in syphilis. On a gross diagnosis, I would say it was an old rheumatic valve. Unfortunately, I did not make any other microscopic sections. I came across this pronounced syphilitic reaction in the aortic cusp in the first sections cut. There was also a great deal of fibrosis in the cusp. I think one big argument against its being rheumatic is that the mitral and tricuspid valves were practically normal. There was little sclerosis of the mitral valve itself, hardly enough to mention. Our English brethren insist that the mitral valve is involved in 100 per cent of the cases of rheumatic heart. The American figures are about 88 per cent. I think it is important to mention this, particularly in reference to Dr Martland's question about the association of mitral stenosis with this anomaly. I did not make an extensive examination of the myocardium for rheumatic involvement, for I did not think it was indicated.

As regards bacterial endocarditis, many of the cases of subaortic stenosis are associated with a bacterial lesion, but the probability is that the bacterial lesion was implanted on the stenosis, because of the similarity of the position of the defect as described in these cases. The uniformity of the ridge in this specimen agrees with the evolution of this anomaly as described by Keith; therefore I am afraid that one would have a difficult time in explaining it on the bacterial basis alone. I think the implantation of a bacterial lesion on it is important, especially with reference to the involvement of the mitral valve portion of this malformation. In most of the bacterial cases reported, that part of the mitral valve was involved, probably by continuity.

**E. LIBMAN** On looking at the specimen, which has just reached me, I note that the thickening is not nearly as marked as it appeared to be from the photograph, and I therefore withdraw what I said about the possibility of the flaps being congenitally thickened. The lesions can be explained by the syphilitic lesion and partly by chemical changes, the deposit of lime.

## FENESTRATIONS OF THE SEMILUNAR VALVES ARTHUR N FOXE

As my paper is largely statistical, I shall not refer to it entirely. A review of the literature reveals how inadequate is the present understanding of the subject. The literature is scant, numeric statistical studies are lacking, and a review of texts of anatomy and pathology shows much confusion as to the nature and frequency of these defects. The results here summarized follow from a study of 300 successively observed hearts.

One or more fenestrations occurred in 82 per cent of the cases. The aortic valve was involved in 188 cases, the pulmonic in 187 cases, a negligible difference in frequency. However, in an estimate of the total number of fenestrations, the pulmonic exceeded the aortic valve in frequency, whereas in the number of leaflets involved, the reverse was true.

From the statistics compiled, it is evident that fenestrations, which are acquired defects, numerically increase with age up to the fourth decade. On the other hand, patent foramen ovale, a distinct developmental defect, numerically decreases with age. There is no evidence to show that fenestrations are developmental defects. Even an inherent weakness of the endocardial or connective tissue is questionable. The fenestrations are a pathologic result fundamentally mechanical in origin. The few present at birth may be acquired from the mechanical effects of the intra-uterine fetal circulation.

A classification of these defects has not thus far been made. The following is such a classification: mechanical (a) circulatory (persistent strain of circulation), (b) traumatic and (c) ulcerative (infection plus erosion of current).

The most frequent cause is the persistent strain of the blood current on the valve leaflets. It is questionable whether the perforations of ulcerative endocarditis or trauma (one case of the latter due to a bullet wound) should be included in a classification of fenestrations. An understanding that they are all fundamentally mechanical in origin would justify such a classification.

The most frequent site is adjacent to the attachment of the free edge of the cusp to the aortic intima. The defects may be single or multiple. They are defects in the endocardium that bridges the gaps between the strands of connective tissue stroma. Less frequently the fenestrations occur along the free edge of the valve. As a result of adhesions of the cusps, they may not communicate with the heart cavity, but form, instead, a passage between two sinuses of valsalva. At times they form a veritable network, not without a peculiar anatomic beauty.

Apart from any esoteric pathologic or anatomic import, have they any clinical importance? Clinical data were lacking in so many cases that it was impossible to correlate any of the observations with murmurs, blood pressure readings, etc. However, in two cases the fenestrations were so large and so numerous as to bring to mind the possibility of aortic insufficiency. In one of these, with a non-dilated orifice, the fenestrations occupied at least one half the valve area.

## DISCUSSION

E LIBMAN I would like to know the percentage incidence for each five year period.

ARTHUR N FOXE There is a defect in these statistics, that is, although age groups are given, each of the groups does not embrace an equal number of hearts, if one bases a conclusion on the cases coming into the Bellevue laboratories there is a larger percentage in the later decades of life. There were forty-two cases observed in persons under 8 years of age, and 258 in those over. There were three fetal hearts, and in this group there were 13 per cent fenestrations per heart. One of the three fetuses had fenestrations, two had patent foramen ovale.

E LIBMAN I do not have any opinion concerning these fenestrations based on personal studies. In Vienna and in Berlin, we were taught that the fenestrations are due to atrophy. I would like to give you the evidence in the literature against this view. What Dr Foxe has presented to us would speak largely against the view that the lesions are entirely congenital. It looks as if some of them, at least, in older persons, may be developed late.

My interest in the subject was aroused by a paragraph in the second edition of the "Lectures on Pathological Anatomy" (1874) by Wilks and Moxon. That made me aware of the fact that fenestrations had been claimed to be of congenital origin. Wilks drew attention to the fact that in certain animals (the shark, for example) the semilunar valves are attached to the wall of the aorta by chordae tendineae. He believed that fenestrations are explainable as remnants of such chordae.

Shortly after I had come across this reference, Dr. Gross showed me a heart which I will now demonstrate to you on the screen. I was shown at first only this flap with this structure, which I recognized as a chordae tendinea. I stated what Wilks had written, and was then shown the other two valves with the fenestrations that you readily see.

Last year I came across an article on this subject by Norman Cheevers in *Guy's Hospital Reports* for 1842. He believed that fenestrations are congenital malformations. I will show you reproductions of his illustrations. One picture is that of a combination of fenestrations and a chordae tendineae, the second shows marked fenestration in the heart of a child, 4 years of age. This large defect in the valve certainly appears to be congenital. The third illustration is of the arrangement of the aortic valves in the shark. There are two sets of semilunar valves, one above the other. The upper is like that in man, while the lower is attached by numerous chordae tendineae.

LOUIS GROSS. I must confess that I was worried about the same problem which evidently worried Dr. Libman, that is, with regard to the significance of the statistics which Dr. Foxe presented, and I was not surprised to hear that his figures on the hearts coming from fetuses and from the lower decades of life are rather small as compared to the later decades. I think that his observations are important, and certainly open up a field to be reinvestigated, but the answer will not be given before Dr. Foxe can compare a relatively large number of hearts representing each decade. When comparisons are made between groups approximately equally large and representing each decade, and if more fenestrations are found in the older decades of life than in the younger, it will be of considerable significance. Apart from this, I must say that the belief that these fenestrations are congenital in origin rather than acquired appeals to me much more strongly. If these lesions are due to pressure or mechanical changes, one ought to be able to find near the fenestrations other thickenings and distortions. One does not. One generally finds these flaps with fenestrations thin and delicate, and not showing any other lesions. This argument may not be pertinent, and I am very glad that Dr. Foxe has brought this question to the fore. I do feel, however, that further work ought to be done along the lines indicated.

ALFRED PLAUT. In case the lesions are due to pressure why are they not much more frequent on the aortic valve than on the pulmonary valve, with the marked differences in pressure at both points?

BENJAMIN SACKS. Only today, I saw a case in which one of the cusps of the aortic valve was almost as large as the other two combined, which were joined together as in the bicuspid aortic valve, but the difference was that the two joined valves, the anterior and the right posterior cusps, were not fused in the usual way. Instead, the commissure was fused for a distance of 4 or 5 mm, and, extending between the commissure and the free edge of the combined cusps, there were chordae-like structures, similar to those which Dr. Libman showed on the screen. In this case, one can only assume that these structures were congenital.

ARTHUR N. FOXE. I see the inadequacy of not having a larger percentage of cases in the younger groups. However, one thing is apparent, that when one examines the hearts of the infants, one observes a marked difference from those of the older groups, and this difference becomes more apparent in the statistical figures.

As to the question why they are not more frequent on the pulmonic than on aortic valves, considering the differences in pressure, it is noteworthy that the

strength of the pulmonic and aortic valves is not exactly the same, and one can distinctly see the differences in density between the leaflets of the aortic and those of the pulmonic valves

As for the statements that these chordae tendineae prove the theory of a developmental origin, I should like to say that they do not. If you will put any picture showing fenestrations on the screen, I will show the inadequacy of the picture from the anatomic point of view, and that these tendineae are not really chordae tendineae from the genetic standpoint. If you take up the heart of an infant, and hold it to the light, you will rarely find fenestrations, here you will find the endocardium, and through the endocardium you will see strands of fibrous tissue that run in this direction from the attachment of the aorta over to the corpora arantii, these strands run in succession to the corpora arantii. These so-called chordae tendineae are nothing more than the remnants of these connective tissue strands. Here you see two supposed chordae tendineae. They are not chordae tendineae. Gradually pressure effects have destroyed the endothelium, and the result is the development of fenestrations.

#### THE MUCOSA OF THE INTRAMURAL SEGMENTS OF THE COMMON BILE DUCT AND PANCREATIC DUCTS BENJAMIN N BERG

The arrangement of the mucosae of the intramural segments of the common bile duct and the major and minor pancreatic ducts was studied in dogs. As the ducts entered the duodenum, there was an abrupt transition from a slightly irregular epithelium to a definite fold formation. As the ducts penetrated deeper into the musculature, villi and septums were encountered. At the papillae, long, slender villi were found arranged in parallel rows. The number of mucous glands was greatly increased. The mucosal pattern was practically identical in the three ducts. The following features were noted: (1) a mucous membrane that practically filled the lumen of the duct, (2) a greatly increased surface area with opportunity for increased mucous secretions, and (3) a mechanical arrangement preventing the influx of duodenal contents into the duct system.

#### DISCUSSION

PAUL KLEMPERER I would like to ask if Dr Berg found lymphadenoid tissue in the terminal portion of the common duct. The question is asked because of the observation of Eppinger of swelling of the lymphatic tissue in the common duct in a case of simple catarrhal jaundice. I have examined repeatedly the terminal portion of the common duct for the presence of lymphatic tissue and have never found it.

BENJAMIN B BERG No, I never did.

#### DETERMINATION OF SUSCEPTIBILITY TO ERYSIPELAS BY SKIN TESTING T R MINER

In the course of the past year at Bellevue Hospital a test for the determination of susceptibility to erysipelas has been employed in a series of 656 persons selected at random from among patients, nurses and interns. The purpose was to determine, first, the incidence of susceptibility and, if possible, some of the factors underlying the apparent lack of resistance among certain persons to this particular form of infection.

The method employed consisted in the intradermal injection into the forearm of 0.1 cc of a 1:500 dilution of erysipelas toxin. An intradermal injection of physiologic sodium chloride solution was used as a control. The readings were made at the end of twenty-four hours, and the degree of susceptibility was determined by the extent of the local reaction.

The age, sex, race, nationality, habits and occupation were noted, together with the disease from which the patient was suffering at the time and such diseases as the patient had had before the test was made that could be attributed to streptococcal infection, namely, scarlet fever, chorea, rheumatic fever and, especially, erysipelas itself.

The total percentage of the susceptible persons was 43, those in the second, third and fourth decades of life giving the greatest number of positive reactions. Females were found to be more susceptible than males in the ratio of 5 to 4. Jews were found to be more susceptible than any other race. By far the greatest percentages of positive reactions occurred among those who worked outdoors where there are varied and variable climatic conditions. Fatigue and exhaustion over long periods of time were also found to play a part, while the great majority of those who gave positive reactions were of careless habits, debauched and unclean.

Perhaps the most significant fact brought out by the skin tests, however, was the relation of susceptibility to erysipelas following previous attacks of the disease and other diseases of streptococcal origin. Of those tested, 3 per cent had previously had erysipelas, and of these, 70 per cent gave markedly positive reactions. In these, the first attack had occurred from two weeks to eighteen years previous to the time of testing the skin, so that the degree of susceptibility is apparently not dependent on the length of time that has elapsed between the initial and the secondary attacks.

Closely following erysipelas itself as a cause of increased susceptibility in subjects, are rheumatic fever and scarlet fever. It was also noted that patients suffering from acute endocarditis, cellulitis and streptococcal infections of the blood stream gave a high number of positive reactions.

#### DISCUSSION

LOUIS GROSS I would like to ask Dr. Miner what he took as an index of susceptibility to erysipelas.

T. R. MINER I took the amount of reaction around the intradermal injection.

LOUIS GROSS First of all, I would like Dr. Miner to explain why he assumes that a positive reaction from an erysipelas toxin necessarily indicates a susceptibility to the disease. You may recall that Dochez and Stevens, and recently Birkhaug, have been able to show, in the cases of the hemolytic streptococcus of scarlet fever and the anhemolytic streptococcus obtained from cases of rheumatism, respectively, that if you sensitize animals by intraperitoneal injections of the so-called toxins of these organisms the animals pass through several phases. In the first phase, the skin of the animals apparently becomes sensitive to the homologous toxin, and early in the first phase one can neutralize this reaction with the homologous serum. Then they pass through an insensitive stage. If you continue to sensitize them, however, you get a third stage in which any organism of the streptococcus group that they employed will elicit a positive skin reaction, which skin reaction cannot be neutralized. In other words, it appears from their work, if one can draw any generalizations from work with these two organisms, that if animals are sensitized for a long enough period they develop a skin sensitivity to the toxins of many organisms in the related and even in unrelated groups, therefore it is not surprising to me, although it is very interesting, that Dr. Miner was able to confirm this in the human being, but I cannot understand why he believes that those giving a positive reaction are necessarily susceptible to erysipelas.

T. R. MINER The testing of the skin to demonstrate susceptibility to erysipelas is identical in principle with that of the Schick or the Dick test, and I think the best way I can answer the question is to state the fact that of the many patients in the erysipelas wards at Bellevue whose conditions clinically were diagnosed as erysipelas, not one gave a positive reaction, we are using that observation on the other side of the erysipelas question, that is, it can be used to indicate a negative diagnosis. If we test a patient's skin, and the test is positive, we can definitely say that the patient does not have erysipelas. If the test is negative, we cannot say that the patient does not have erysipelas. Every patient in the wards who was definitely proved to have erysipelas gave a negative reaction in the skin test.

## PHLEGMONOUS GASTRITIS (ERYSIPELAS OF STOMACH?) HARRISON S MARTLAND

Recently, I had the opportunity of observing before death, and of finding at autopsy, a case of phlegmonous gastritis of streptococcal origin in which the appearance of the stomach, as seen with the naked eye, suggested the possibility of the condition being erysipelas. The histologic observations were identical with those seen in erysipelas of the skin or that of the mucous membranes. The streptococcus occurring in enormous numbers in the submucosa was sent to Birkhaug for complete identification.

The stomach was taken, at autopsy, from a white woman, aged 72, who had been sick for one week and had died five hours after admission to the hospital. At the beginning of her illness, she was suddenly seized with cramplike pains in the abdomen, localizing in the upper left quadrant. She was nauseated and vomited twice. The pain became intense, the abdomen being distended and tympanitic. A suspicious mass was felt in the left hypochondrium. Only stimulative treatment was given at the hospital. A clinical diagnosis of peritonitis possibly due to a malignant condition of the abdomen was made.

At autopsy, the stomach was greatly distended. Near the pylorus, it felt as if there was a large stenotic growth. The whole stomach wall was leathery and did not collapse. Enlarged glands were not present along the lesser or the greater curvature, and enlargement of periportal nodes was not seen. The esophagus was normal. On opening the stomach, which was empty, a remarkable condition was seen. There was marked thickening, with edema of the stomach wall, most marked in the pyloric half, where the wall was  $\frac{1}{2}$  in (1.27 cm) thick. The mucosa was a diffuse scarlet, and showed only an occasional mucosal and submucosal hemorrhage. The rugae were obliterated and ironed out by the edema. Recent or cold ulcers and macroscopic abrasions were not observed. Close inspection of the stomach wall showed that over half of the thickening was due to distention of the submucosa by a watery, purulent exudate. The mucosa was but slightly swollen. In the submucosa, lying between the mucosa and the internal circular muscular coat, which was plainly visible, there was a large amount of grayish, watery, purulent fluid, which could be pressed out. The submucosa had a somewhat honey-combed appearance, owing to a partitioning off of this purulent fluid by connective tissue trabeculae. In places, multiple small abscesses were seen in which the fluid was thicker and more creamy. The muscularis, aside from the presence of edema, was grossly free from pathologic evidence. Over the serosa was a plastic purulent exudate. This suppuration extended diffusely throughout the entire submucosa of the stomach, but was more pronounced in the pyloric half. It was sharply demarcated above by the esophageal orifice and below by the pyloric valve. The mucous membrane of the esophagus and the duodenum was normal. There was considerable purulent fluid in the pelvis and abdominal gutters and an extensive fibropurulent exudate over the stomach and the loops of the small intestine, gently gluing them together in places.

Microscopic sections made through the entire thickness of the stomach wall showed that the mucosa was intact and only slightly edematous, it was practically free from any cellular exudate. The muscularis mucosa was intact, but in places edematous and swollen, and it showed a slight infiltration with lymphocytes and histiocytes. The submucosa was greatly thickened, forming over half the entire thickness of the stomach wall. Its inner portion was comparatively free from cellular exudate but showed enormous edema, the fluid distending the tissue spaces and widely separating them. The little amount of cellular exudate present was composed chiefly of lymphocytes and monocytes. A definite relationship to the lymphatics could not be made out. Few polymorphonuclears were present. As one approached the middle of the submucosa, the exudate became abundant and more polymorphonuclears were present. This became so marked as to form small abscesses. The periphery of these areas was formed chiefly of lymphocytes and monocytes, and the central portions contained chiefly polymorphonuclears. In the center of many of these areas there was extensive necrosis with numerous poly-

morphonuclears and considerable cellular detritus. Gram stains showed numerous streptococci in these areas, they were scant or absent in other portions of the stomach wall. Near the internal circular layer of the muscularis there was a strong defense wall composed of many histiocytes and lymphocytes and few polymorphonuclears. In places, this cellular exudate filtered through the muscle bundles of the muscularis and extended to the serosa, where there was edema with beginning suppurative peritonitis. The muscularis itself was free.

Smears made from the fluid pressed from the submucosa of the stomach showed a great number of gram-positive streptococci.

A case of phlegmonous gastritis has been described, in which the appearance of the stomach is identical with that in most cases of diffuse so-called idiopathic phlegmonous gastritis. That is, there were not any gross lesions of the mucous membrane such as ulcer, carcinoma, abrasions or other injury. The condition was diffuse throughout the entire stomach and almost entirely limited to the submucosa. The diffuse blushing of the mucosa, the ironing out of the rugae by edema and the thick, edematous condition of the submucosa, which was filled with a watery, grayish fluid containing innumerable streptococci with the occasional formation of small abscesses suggested the gross appearance of erysipelas, and the condition was similar in every way to extensive erysipelas of the skin with cellulitis of the subcutaneous tissues. The sharp demarcation of the suppurative process in this case by both the cardiac orifice and the pylorus, areas both of which have a mucosa that is rather tightly bound down, was similar, for instance, to the sharp demarcation and stoppage of facial erysipelas at the lower border of the mandible.

Histologic examination showed the lesion almost entirely confined to the submucosa. It was characterized by extensive boggy edema, in which the cellular exudate was composed chiefly of lymphocytes and monocytes. The polymorphonuclears were abundant only in the central areas, in which formation of abscesses had occurred, and in which there was necrosis, cell detritus and innumerable streptococci. This histologic picture is identical with that seen in erysipelas.

(An agar slant containing a pure culture of a gram-positive hemolytic streptococcus, recovered from the submucosa after autopsy by Dr. Lloyd Riggs, was sent to Dr. Konrad E. Birkhaug, associate professor of bacteriology at the University of Rochester, N. Y., for identification. At the time of the presentation, Dr. Birkhaug's opinion had not been received. A complete identification of the streptococcus as belonging to the serologic types of *Streptococcus erysipelatis* was later made by Dr. Birkhaug. The strain was unsuitable for agglutination because of its quick spontaneous precipitation in broth during the first ten hours of growth. He then resorted to absorption of known antibodies of *S. erysipelatis* and found that the strain removed the agglutinins for three of four of his standard strains of *S. erysipelatis*, and removed only to a slight extent the agglutinins from an antiserum of *Streptococcus scarlatinae*. The strain also gave rise to a production of toxin in Douglas' tryptic digest broth. In a series of titrations in the skin of persons susceptible to the toxin of *S. erysipelatis*, he found that a potent exotoxin was produced, 1 cc. of which contained more than 10,000 skin test doses. In proper dilutions with the antitoxin of *S. erysipelatis*, this toxin was completely neutralized. As a result of Dr. Birkhaug's painstaking confirmation, this case is reported in full as one of erysipelas of the stomach.)

#### DISCUSSION

PAUL KLEMPERER. Phlegmonous gastritis is actually rare. I still remember a specimen shown us when I was a student. It was an impressive picture. The last time I observed a case was years ago in the New York Post-Graduate Hospital. In that case, there was a small carcinoma at the cardia. The submucosa was markedly thickened, and on the serosa the lymph vessels stood out distinctly as yellow strands. This was due to their filling with polymorphonuclear leukocytes. The infiltration of the submucosa was also leukocytic. In addition, I recall another case in which only a part of the stomach was phlegmonous. In the vicinity



of a carcinoma there was an area from 3 to 4 cm wide, which contained pus. I think the question can be brought up again whether it is possible for patients with phlegmonous gastritis to recover and whether cases of the benign leather-bottle type could not be the result of such an occurrence.

**NICHOLAS ALTER** There was a case at the Post-Graduate Hospital in which an operation for pyloric obstruction was performed. In that case, the stomach was uniformly thickened and presented the picture of a leather-bottle stomach. The pyloric region was greatly hypertrophied. Resection of the stomach was done, and the patient recovered. The stomach did not show any ulceration, but a uniform thickening of the wall, and the coats were considerably hypertrophied, mostly the muscle. The submucosa was edematous and fibrous, and the mucosa swollen. The microscopic picture showed a marked infiltration with eosinophils, neutrophils were absent. The condition was diagnosed as a subacute phlegmonous gastritis. The patient made a good recovery, and is still well. I make this remark only to answer Dr Klemperer's question as to whether these conditions ever heal and result in a so-called benign linitis plastica.

**BENJAMIN SACKS** In the pathologic museum at Mount Sinai Hospital there is a specimen of phlegmonous gastritis, to which it was Dr Libman's practice to refer as erysipelas of the stomach.

**HARRISON MARTLAND** Evidently there are various types of phlegmonous gastritis, according to what we have heard. In Dr Klemperer's case, it was probably secondary to carcinoma, and in this respect his case is similar to some of the cases described in the literature. The cellular elements in the exudate were chiefly polymorphonuclears in contradistinction to their scarcity in my case. In Dr Alter's case the condition was evidently more of a subacute process. Eosinophils were not present in my case. The histologic picture, as I have tried to describe it, was similar to that seen in erysipelas of the skin. The polymorphonuclears were not so abundant as the lymphocytes and the histiocytes, and the process was almost entirely limited to the submucosa. If the streptococcus isolated from my case can be positively identified as belonging to the group of *Streptococcus erysipelatis*, I believe that, taken in conjunction with the gross appearance of the stomach and the character and location of the exudate microscopic examination, the condition warrants a diagnosis of erysipelas of the stomach.

#### DEMONSTRATION OF FOUR CASES OF MENINGOCOCCUS SEPTICEMIA WITHOUT MENINGITIS. PAUL KLEMPERER

These cases occurred in children of 4 and 14 months and of 4 and 14 years of age. The clinical course was that of a fulminating disease of from twelve to fourteen hours' duration, starting with vomiting and fever. All the cases showed petechial spots on the skin, but only in the two infants was the clinical picture dominated by the purpuric eruptions. The necropsy of these two cases revealed a hemorrhagic infarction of both suprarenal glands. The two other cases showed multiple ecchymoses of the serous membranes, mainly on the peritoneal surface, and small petechiae of the mucous membranes of the gastro-intestinal tract, ureters and bladder. The mesenteric lymph nodes were swollen and hemorrhagic. The results of the bacteriologic examination of heart blood, spleen and spinal fluid were negative. The latter was perfectly clear.

The histologic examination revealed the presence of large quantities of gram-negative diplococci within the small arteries, arterioles and capillaries of the corium, frequently phagocytosed by leukocytes. There was extravasation of blood around the capillaries and often a mild infiltration by polymorphonuclear leukocytes and histiocytes. Within the submucosa of the intestinal tract, foci of perivascular leukocytic infiltration and hemorrhage were found. Here the small arteries showed circumscribed destruction of the wall with localized endothelial proliferation. Within such foci, gram-negative diplococci were found. There were also circumscribed lesions within the myocardium consisting of polymorphonuclear leukocytic infiltration and necrosis of muscle fibers, which also contained the same organism.

The suprarenal glands showed only an enormous congestion of the cortical capillaries and diffuse extravasation of blood

## DISCUSSION

J H GLOBUS The main facts have already been presented. You were told of the clinical manifestations and the general anatomic alterations and the lack of any evidence of pathologic changes in the brain. To recapitulate, first let me stress the fact that the cases all showed definite neurologic manifestations. They were all regarded clinically as neurologic cases. They all started acutely with symptoms pointing to involvement of the central nervous system: vomiting, convulsion, deep stupor and some bulbar signs. They all resulted fatally within the short period of from twelve to fourteen hours. They were all regarded at the time of autopsy as instances of poliomyelitis, because they occurred at the time when an epidemic of poliomyelitis was regarded as occurring in the city. Only when we began to study them histologically was doubt aroused as to the diagnosis of poliomyelitis, and we began to look around for some other explanation for the grave neurologic picture.

I have here three slides. The first shows only one thing—I believe it is a positive sign: the marked distention of the perivascular spaces with the marked retraction of the surrounding tissue, leaving behind some of the glia fibers still attached to the vessel wall. This distention is apparently due to the marked edema. Another change is the marked increase in the number of oligodendroglia cells, the latter have a clear area around the nucleus—a clear perinuclear area. This is not just an edematous space, such as is found in a toxic degenerative process of the brain. It is part of the cell body, and Penfield described this peculiar change in the glia cells as an acute swelling of the oligodendroglia.

In another section from another case, we see a marked distention of the perivascular space, with a number of oligodendroglia cells migrating toward the vessel wall. It is also a common manifestation of toxic degenerative changes in the brain.

Here is another preparation showing the only vessel found in the study of almost forty or fifty different blocks taken from various portions of the brain—the only vessel which shows moderate perivascular infiltration. This was the only section in the entire group of cases—the only section out of a total number of forty blocks—with an inflammatory lesion in the meninges.

With these few facts in mind, I should like to call to your attention a paper read by Symmers and Brown three years ago. They described a disease as acute serous encephalitis. They described changes of just the type I have shown you, with no perivascular infiltrations, with no evidence of meningeal involvement, with nothing but distention of the perivascular spaces and edema of the brain. Clinically, all of these cases, eleven or twelve, were true to type: an acute onset, fulminating course, convulsions, various bulbar symptoms and finally deep stupor and death within the short period of from twenty-four to forty-eight hours. Symmers and Brown regarded these cases as an extremely acute fulminating type of acute epidemic encephalitis. Under the circumstances, it was perhaps right to group them as epidemic encephalitis, but I think we may put another interpretation on them, for here we have a clinical picture and anatomic manifestations exactly of the type described by Symmers and Brown, but, in addition, we have evidence of a meningococcemia. The changes in the brain are apparently secondary to a general meningococcemia.

DR GOLDBURG Could not this picture and the pathologic changes in the brain occur with any general bacteriemia?

J H GLOBUS I have said that the picture in the brain may occur in any form of bacteriemia or toxemia, and is not pathognomonic for meningococcemia.

E LIBMAN In cases as severe as those described by Dr Klemperer, I would have looked for positive results in the blood cultures. Perhaps a sufficiently large amount of blood could not be withdrawn. In some of these cases the diagnosis may be made with ease by puncturing the lesions of the skin and staining

the material obtained, or by studying stained sections of them. The earliest results obtained by an examination of the blood obtained by puncture were those of Netter and his pupils. Ludwig Pick was the first to find the cocci in stained sections of the hemorrhagic lesions.

In some cases of general meningococcus infection in infants, the lesions are firm, like some of the lesions seen in cases of scurvy, and a mistake in diagnosis may easily occur. In cases of meningitis in infants, rigidity of the neck may be absent. The same is true of cerebrospinal meningitis in old people, but to a less extent than in infants.

PAUL KLEMPERER. In two cases a large amount of blood was taken for culture, with negative results, in one case, 30 cc, taken immediately after death, was cultivated but remained sterile, and in this case an innumerable number of cocci were found within the blood vessels of the skin and even in smears taken after death. It seems as though the cocci die rapidly within the circulation. I examined petechial spots in two other cases of meningococcus septicemia without meningitis in which the patients recovered after treatment, and in these cases meningococci were not present within the vessels, but I found the same vascular changes as in the case with cocci. Apparently, the meningococci may disappear early after having produced the vascular lesions.

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## CHICAGO PATHOLOGICAL SOCIETY

*Regular Monthly Meeting, Nov 12, 1928*

ESMOND R. LONG, *President, in the Chair*

### THE RETICULO-ENDOTHELIAL SYSTEM IN *BARTONELLA* INFECTIONS OF ALBINO RATS. PAUL R. CANNON and PRESTON H. McCLELLAND

The significance of the reticulo-endothelial system as a mechanism of defense against infections has been emphasized with increasing frequency during recent years. Most studies have dealt with its relationship to antibody production, and comparatively few attempts have been made to determine the rôle of this system in its reactions to actual disease conditions. *Bartonella* infections of albino rats, therefore, appeared to offer an unusual opportunity for such a study.

The spleen ranks first of the organs of the reticulo-endothelial system among mammals as the one richest in histiocytes. But even here, there appear to be differences in species as to the relative amount. Krumbhaar has recently shown that when the ratio of the spleen weight to the body weight is used as an index, the spleen is relatively of more significance in man, the dog and the rat, less so in the monkey and the guinea-pig and least in the cat and the rabbit. It is suggestive that most of the earlier work on the effects of splenectomy on antibody formation was done with rabbits and guinea-pigs, animals in which the spleen, quantitatively, appears to be of least significance.

The so-called *Bartonella* anemia of rats offers perhaps the most outstanding example of the dominant importance of the spleen in controlling a latent infection. This anemia occurs in infected rats after the removal of the spleen, due, presumably, to a recrudescence of the *Bartonella virus*. The removal of one or both suprarenal glands, one or both testes, the omentum, the cerebrum or the thyroid gland has no effect, splenectomy, however, causes the typical anemia. One third of the spleen appears to protect. When the pedicle of the spleen is ligated, the organ excised and placed in the peritoneal cavity, the anemia develops as with splenectomy, indicating the necessity of an intact blood supply to control the virus.

The size of the spleen is significant in infected animals as compared with uninfected ones. The average ratio of the spleen weight to the body weight for eighty-four rats infected with the *Bartonella virus* is 0.74 per cent. My figures for thirty-four uninfected Wistar Institute strain animals is 0.25 per cent. The

differences between the ratio of the spleen weight to the body weight in rats infected with *Bartonella* and normal uninfected rats is so striking that it is frequently possible to tell by the splenomegaly alone whether or not the animal is infected

Histologically, there is definite evidence of the reaction of the reticulo-endothelium of the spleen to *Bartonella* infection. Spleens from normal uninfected Wistar strain rats are small and firm, and the splenic follicles are compact and composed mainly of lymphocytes, with only a slight hyperplasia of the centers of the follicles and without mitosis. Also, there is a narrow marginal zone of histiocytic tissue merging into the splenic pulp. On the other hand, spleens from animals infected with *Bartonella* are large and fleshy; microscopically, the splenic follicles are large and hyperplastic as shown by the conspicuous germinal centers with many mitotic figures, together with a broad marginal zone which fuses with the prominent splenic pulp.

There can be little question, therefore, that the spleen in some way keeps the *Bartonella* virus under control as a latent infection. When this inhibitive influence is removed, the virus apparently develops rapidly with the resulting acute anemia. It is conceivable that the spleen, as an important part of the reticulo-endothelial system, exerts its controlling effect either by phagocytosis of the *Bartonella* virus at a constant rate, by the formation of antibodies of some type which restrain the development or destroy the organisms, or by both. Thus, when the balance is disturbed between the offensive powers of the organism and the defensive mechanisms of the host, the infection flares up and the anemia results. It is evident, therefore, that the "factor of safety" resides in the spleen, equalling approximately two thirds of this organ, the removal of this factor of safety allows the disease to progress.

If these assumptions are correct, saturation of the cells of the reticulo-endothelial system as a whole to as marked a degree as possible with particulate matter should lead to similar results. With this in view, suspensions of Higgins' india ink in isotonic salt solution were injected into normal rats and into others with the *Bartonella* virus. The results demonstrated clearly that adequate blockade of the reticulo-endothelial system in rats infected with *Bartonella* is followed by a relapse of *Bartonella* infection with the development of anemia as with splenectomy. In order to block this system successfully, however, a maximum of material must be injected within a short time so as to prevent a compensation by regeneration of the cells. Intravenous injections of suspensions of india ink, twice daily, apparently prevented this. Under these conditions, animals infected with the *Bartonella* virus as a latent natural infection developed the typical anemia, whereas normal uninfected Wistar strain rats remained practically normal.

These experiments demonstrate the importance of the spleen in a mammal as an organ of defense against an infectious disease in a latent stage. Furthermore, they indicate the influence of the reticulo-endothelial system as a whole in protecting the host against infection.

#### DISCUSSION

FRANK A. MCJUNKIN. Was the phagocytic activity of the splenic cells as great without as with the carbon particles? Cells stimulated with trypan blue, although large, take up much greater quantities of particulate matter than those not so stimulated.

HARRY A. SINGER. Does a vitamin deficient diet cause the *Bartonella* type of anemia?

R. H. JAFFE. I was unable to cause mobilization of the *Bartonella* virus by deficient diets. Have studies been made to find the latent focus of the *Bartonella* virus?

P. R. CANNON. We did not kill the rats immediately after injecting the carbon, so we are unable to say anything about the erythrophagocytosis. Koessler and Maurer fed vitamin deficient diets to rats, but the resulting anemia is unlike that caused by *Bartonella*. With a diet deficient in vitamin B a *Bartonella* relapse

has not been obtained By methods for demonstrating the *Rickettsia* bodies attempts are being made to find the latent foci

E R LONG These studies indicate the hazards of using animals at random, because of such latent infections

STUDIES ON AN ORGANISM ISOLATED FROM THE PAROTID DUCT IN EPIDEMIC PAROTITIS RUTH E TAYLOR

The results are reported from cultures of parotid secretion in thirty-one cases of mumps and in ten control cases A green-producing streptococcus was found in 83.9 per cent of the cases of mumps The organism was not found in any of the control cases The parotid secretions were examined for the spirochete described by Kermorgant (abstr, J A M A 85 392 [Aug 1] 1925) but none was found

Attempts to demonstrate a relationship between the green streptococcus and mumps by means of immune reactions failed Herb's (Arch Int Med 4 201 [Sept] 1909) results as to experimental parotitis were not confirmed, although the organism she described resembled that found in this series culturally and morphologically The organism which was isolated from the cases studied was shown to be pathogenic for cats, but no convincing experimental mumps was produced in these or in other animals

DUBOIS' SEQUESTRUMS (NONSYPHILITIC) OF THE THYMUS E L BENJAMIN

Dubois' abscess of the thymus gland was first described as a product of congenital syphilis, in 1850 Hammar and Hart, Tuve, Eberle and Oliver also believed them to be the result of a congenital syphilitic vascular disturbance The presence of *Spinochacta pallida* was demonstrated by Simmonds and Schridde Hammar spoke of them as sequestrum cysts (circumscribed regions of necrosis of the parenchyma of the thymus) lined by epithelium derived from the ectodermal reticulum Eberle believed them to be dilated epithelial channels, remnants of the thymus anlage, with a subsequent collection of pus in these channels Chiari and Schlesinger held the opinion that the abscess was a cyst formed by Hassall's bodies invading the thymus tissue Materna described a Dubois abscess in the thymus of an African negro, aged 24, who was suffering from relapsing fever There were spirochetes (Dutton) in the wall of the abscess This case was questioned by Lubarach and Schmincke

Dr R H Jaffe performed an autopsy on the body of a full-term, white, male infant, aged 3 days, twenty-two hours after death Clinically, the infant had symptomatic hemorrhagic purpura immediately after ligation of the umbilical cord The presence of disseminated petechial hemorrhages in the skin, mucous membranes and leptomeninges, hemorrhagic extravasations in the lungs, liver and kidneys, multiple Dubois' sequestrum abscesses of the thymus gland, hyperplasia of the spleen (29 Gm), hyperplasia of the mesenteric and peribiliary lymph glands, and fibrinous perisplenitis and icterus established the diagnosis of symptomatic purpura hemorrhagica

The thymus weighed 15 Gm, was dark red, firm and measured 6 by 4.5 by 1.5 cm On the surfaces made by cutting there were numerous irregular soft yellow regions of necrosis, varying in size from that of a pinpoint to 2 by 12 mm in diameter Microscopically, the normal structure of the thymus was obscured, being composed of a variety of myeloid, lymphoid and nucleated red cells In the yellow places there was a coagulation necrosis of the parenchyma with calcium deposits The necrotic lymphocytes were visible, and a leukocytic reaction was absent These foci were sharply demarcated and surrounded by reticulum cells arranged in several layers The smallest foci were devoid of such a lining Spirochetes were not found in the thymus, spleen or suprarenal glands Specific syphilitic lesions were absent

The mother, aged 25, was living and well This child had been her third full-term child The other two were living and well, the youngest 1 year old The

only pertinent data in the maternal history were a thyrotoxicosis from the second to the seventh month of this pregnancy, the petechia reaction of the skin after the application of a constrictor (two days post partum), the escape of a brown amniotic fluid when the membranes were ruptured, and the absence of any signs of syphilis

The Dubois' sequestrums apparently were not caused by syphilis but were the result of sepsis developing from an intra-uterine infection, possibly associated in some manner with the thyrotoxic crisis of the gravid mother, as evidenced by the syndrome of symptomatic purpura hemorrhagica

#### SPONTANEOUS RUPTURE OF THE AORTA RICHARD A. LIVVENDAHL

Two specimens with spontaneous rupture of the aorta were presented. In both the lesion occurred one and one-half fingers above the aortic cusps. The gross appearance of the vessels were those of slight atheromatous changes, without wrinkling or puckering of the intima. However, the histologic examination revealed typical syphilitic alterations resulting in marked diminution of the functional capacity of the muscular and elastic tissue structures. Perforation occurred into the pericardial sacs, which were markedly distended by blood. Arteriosclerosis was generalized, but most marked in the kidneys, with secondary hypertrophy of the heart. Clinically, both patients had a sudden onset of severe precordial pain and dyspnea, also an elevated blood pressure. The importance of careful microscopic examination of different portions of the aorta was emphasized. The previous literature and the etiologic factors were discussed.

#### DISCUSSION

H. A. SINGER: Why are the spontaneous ruptures of the aorta in the first portion of the arch, as you say, and at the aortic end of the ductus Botalli? What is the hydrostatic pressure necessary to rupture the aorta?

P. R. CANNON: Were these patients under active antisyphilitic treatment?

R. H. JAFFE: The predilection sites for rupture are at the two fixed places of the aorta.

E. R. LONG: Is there a possibility that these lesions are rheumatic in origin instead of syphilitic?

R. A. LIVVENDAHL: Active antisyphilitic treatment was not in use. With dead aortic tissues 1,074 mm of mercury has been reported necessary for rupture.

## Book Reviews

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LECTURES ON CONDITIONED REFLEXES Thirty-five years of Objective Study of the Higher Nervous Activity of Animals By IVAN PETROVITCH PAVLOV, M D, Director of the Physiological Laboratories, Institute of Experimental Medicine and Academy of Sciences, formerly Professor of Physiology, Military Medical Academy, Leningrad Translated from the Russian by W Horsley Grant, M D, B Sc, with the collaboration of G Volborth, M D Price, \$6 50 Pp 414, with bibliography and index New York International Publishers, 1928

Pavlov is universally recognized as the pathfinder and leading experimental explorer in the field of nervous physiology and animal and human behavior, that is now considered under the term "conditioned reflexes" Conditioned reflexes are those associations developed after birth as a result of the individual experience and learning of the person or animal as distinct from the simpler and more or less invariable reflexes that are laid down in the structural relations and are therefore inborn The problem of the analysis and control of conditioned reflexes is therefore of the highest practical importance for educational progress and social control

The present volume is a translation from the Russian of a series of papers and addresses delivered by Pavlov before various medical and scientific organizations since as early as 1903 It is not, therefore, a book or monograph in the usual sense, containing progressive development of the whole theme Since it is a translation of different addresses based on research work by students of Pavlov in his own laboratory, there is necessarily a good deal of repetition and overlapping in the different chapters

The greatest shortcoming in the book, however, is the practically complete absence of references to investigations in the same field but in laboratories other than Pavlov's These parallel investigations usually confirmed but sometimes disagreed with Pavlov's observations in particular lines and frequently there were different interpretations from those of Pavlov It would have been interesting and valuable to have had the review and reaction of the aged investigator to the entire aspect of conditioned reflexes up to the year 1928 One must be grateful, however, to have at least the main body of the contributions from Pavlov's own laboratory accessible in English

There is an interesting initial chapter dealing with the life and education of Pavlov This biographical sketch and the prefaces occupy the first forty-six pages of the book The bibliography at the end contains a fairly complete citation of all the publications on the subject of conditioned reflexes from Pavlov's own laboratory in Petrograd It is interesting to note that practically all these publications appear under the names of Pavlov's students, only occasionally does Pavlov's own name appear on a title On examination of this final volume by the 80 year old investigator, the reader who recalls Pavlov's first researches on the digestive glands for which he received the first Nobel prize awarded in the medical sciences, is impressed with the continued high quality and mental activity disclosed He is also impressed with the fact that Pavlov has become more speculative and philosophical with advancing years This adds to the interest which the book has for the general reader, but it scarcely adds to the progress of objective science The two short chapters on "The Reflexes of Purpose," and "The Reflexes of Freedom" are an instance of this fact They contain interesting speculations but virtually no objective experimentation that would warrant their inclusion in a monograph on experimental science

The present volume is one of great interest to the physician, the biologist, the educator, the psychologist and, in fact, to every educated man The book is not in any sense the final word On some phases of the subject, parallel investigations in other laboratories have questioned facts and nullified interpretations found

in the present volume That is to be expected in a field as complex and new as that of conditioned reflexes The critical reader, while not overlooking these defects, will forget them in contemplating, as Professor Cannon says, "the splendid example of industry and devotion to science which the first explorer in the field of conditioned reflexes has given during his long life, and this will be an incentive to those who follow after him and push further into the unknown"

UEBER DAS PROBLEM DER BOSARTIGEN GESCHWULSTE EINE EXPERIMENTELLE UND THEORETISCHE UNTERSUCHUNG VON PROFESSOR DR. LOTHAR HEIDENHAIN Paper Price, 27 marks Pp 153, with 141 illustrations Berlin Julius Springer, 1928

Experimental oncology of today is dominated by two essential facts (1) cancer can be induced by multiple factors such as tar, arsenic, aniline, soot, roentgen rays, embryonic tissue, nematodes, and bacteria and (2) cancer is "specific," that is, the disease cannot be transmitted from one animal species to another Even more, within the same species, such as chicken, pigeon and duck, experiments on transmission of the disease have failed up to the present time Heidenhain in his monograph emphatically states that cancer is infectious in origin being always caused by one living germ He also affirms that he was able to transmit cancer from man to mouse and that cancer and sarcoma are caused by one and the same factor In his opinion, the occurrence of one or the other variety of tumor depends on whether the causative agent happened to attack the epithelium or the mesenchymal tissue

Heidenhain assumes *a priori* that the cancerogenous virus is enclosed within the tumor cells, and he gives his method of "freeing" it, which is as follows One gram of tumor tissue mixed with 9 cm of physiologic sodium chloride is ground in a meat grinder This is overlaid with a layer of toluene and kept for ten days in the incubator at 37 C, after which period the incubated mixture (Warme-Autolisate, or W-Autole) represents a "formless detritus" ready for use One-half cubic centimeter of this W-Autole is then injected into the inner surface of the thigh of the mouse, or 0.2 cc in the liver or peritoneum, respectively

The material as referred to consisted of tissue from cancer in man, mammary cancer in most instances, which was used on over 2,000 mice (The statistics are only preliminary) Of this number about 7 per cent developed tumors which Heidenhain considers as being malignant in nature, being of course produced by the "Autole"

The experiments are interesting in many other ways 1 The tumor never developed at the site of inoculation, but in organs or structures far remote from the point of inoculation, which is due to "the lymphatic or hematogenous transmission of the virus" 2 Most of the obtained tumors were sarcomas 3 Only a few tumors gave metastases (Nur wenige Male hatten wir dies Glück to find metastases) 4 The transmitted tumor in the mouse did not usually resemble the mother tumor 5 Autolysates from carcinomas gave rise to sarcomas and vice versa

That cancer can be induced by bacteria (which probably play rather a predisposing than a determining role for the development of a malignant disease) was referred to in this treatise and is recognized by every observer But the notion that the essential cause of cancer in general is a microscopic virus was not borne out by any research up to the present time Heidenhain's work does not add any new data to this problem In the first place, the small percentage of positive results obtained by him do not warrant sweeping conclusions In the second place, possibility that the tumors in Heidenhain's stock of mice were of spontaneous origin cannot be excluded Finally, a close examination of the abundant photomicrographs, which illustrate the luxuriously edited monograph, reveals, in many instances, ambiguity as to the blastomatous nature of the condition found by the author



A SHORT HISTORY OF MEDICINE, INTRODUCING MEDICAL PRINCIPLES TO STUDENTS AND NON-MEDICAL READERS CHARLES SINGER, M D, D Litt, Oxford Fellow of the Royal College of Physicians of London and Lecturer on the History of Medicine in the University of London Price \$3 Pp 368, with 142 illustrations New York Oxford University Press, 1928

The purpose of the author is to give a simple, elementary account of the history of medicine as a science The book is divided into six parts that deal with the following periods Ancient Greece (to about 300 B C), the heirs of Greece (300 B C to about A D 200), the Middle Ages (A D 200 to 1500), the rebirth of science (1500-1700), the period of consolidation (1700 to 1825), and the period of scientific subdivision (1825—) More than half of the book is devoted to modern medicine

The story of the scientific side of medicine is told lucidly and interestingly Stress is laid on the development of the underlying principles rather than on actual practice Consequently, the biographical element and details of the status and training of physicians are kept in the background

In the preface, the author invites corrections or suggestions In response, it may be pointed out that the statements about the cause of yellow fever need revision, that August von Wassermann and Alphonse Laveran, listed as living, are dead, and that it is surprising that the scientific side of dentistry did not receive any consideration

The illustrations are taken from many sources, they are all instructive and some are of unusual interest Dr Singer's work should attract the medical reader as well as educated persons without special medical knowledge It is warmly recommended to the medical student and to the young physician

AUSGEWAHLTE SCHRIFTEN ZUR TUBERKULOSEPATHOLOGIE By K E RANKE Edited with an introduction by W Pagel and M Pagel Price, 20 marks Pp 236, with 25 illustrations Berlin Julius Springer, 1928

The plan of Ranke to collect his scattered investigations and treatises on tuberculosis in monograph form, prevented by his untimely death in 1926, has been carried out in part by admiring colleagues The two Pagels have selected from Ranke's numerous writings those in which he developed the doctrine of the primary complex and three stages in tuberculosis The investigations and line of reasoning which carried Ranke from pure morphology to far-reaching views on immunity in tuberculosis have stimulated a great deal of discussion and controversy The Pagels point out that this has been based frequently on an inaccurate knowledge of Ranke's own views, much of his earlier work not being readily accessible The present volume is put out with the intention of obviating this difficulty Slight changes from the original publications are indicated by italics, and only those changes are included which Ranke himself had intended The volume, aside from its value as a collection of selected writings from the pen of a great phthisiologist, should fulfil the stated purpose of the editors

## Books Received

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CONSTITUTIONAL INADEQUACIES An Introduction to the Study of Abnormal Constitutions By Nicola Pende, M D, Professor of Clinical Medicine, Royal University of Genoa, Italy Translated by Sante Naccarati, M D, Sc D, Ph D, Associate Professor of Nervous and Mental Diseases, New York Post-Graduate Medical School With a Foreword by George Draper, M D, Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, and Chief of Constitution Clinic, Presbyterian Hospital, New York City Cloth Price, \$3 50 Pp 270, with illustrations Philadelphia Lea & Febiger, 1928

ORGANIC LABORATORY METHODS BY THE LATE PROFESSOR LASSAR-COHN An Authorized Translation from the General Part of the Fifth Revised Edition By Ralph E Oesper, Associate Professor of Analytical Chemistry, University of Cincinnati Edited by Roger Adams, University of Illinois, and Hans T Clarke, formerly of the Eastman Kodak Company Number two of The World Wide Chemical Series edited by E Emmet Reid, Professor of Organic Chemistry, The Johns Hopkins University Price, \$6 50 Pp 458, with illustrations Baltimore Williams & Wilkins Company, 1928

BULLETIN OF THE NATIONAL RESEARCH COUNCIL, NUMBER 66 Funds Available in the United States for the Support and Encouragement of Research in Science and its Technologies Second Edition Compiled for Research Information Service by Callie Hull and Clarence J West Price, \$1 Pp 90 Washington, D C The National Research Council of The National Academy of Sciences, 1928

BULLETIN OF THE NATIONAL RESEARCH COUNCIL, NUMBER 65 Bibliography of Bibliographies on Psychology from 1900 to 1927 Compiled by C M Louttit for the Research Information Service of the National Research Council Price, \$1 50 Pp 108 Washington, D C The National Research Council of The National Academy of Sciences, 1928

A SHORT HISTORY OF MEDICINE, INTRODUCING MEDICAL PRINCIPLES TO STUDENTS AND NONMEDICAL READERS By Charles Singer, M A, M D, D Litt, Oxford, Fellow of the Royal College of Physicians of London, Lecturer on the History of Medicine in the University of London Price, \$3 Pp 368 New York Oxford University Press, 1928

METHODS AND PROBLEMS OF MEDICAL EDUCATION, SERIES XI Intended for distribution to teachers and administrators in medical schools and hospitals Separate reprints and a limited number of volumes are distributed gratis by The Rockefeller Foundation Pp 263 New York Division of Medical Education, The Rockefeller Foundation, 1928

ABSTRACTS OF THESES IN SCIENCE, SERIES V Ogden Graduate School of Science Submitted to the Graduate Faculty of the University of Chicago for the degree of Doctor of Philosophy, from September, 1926, to June, 1927 Price \$3 Pp 461 Chicago The University of Chicago Press

ÉTUDE DE LA REACTION DE VERNES A LA RESORCINE DANS LE DIAGNOSTIC ET LE PROGNOSTIC DES TUBERCULOSES Comparaison avec la reaction de fixation Andre Breton, ancien interne des Hopitaux de Lille, Preparateur a L'Institut Pasteur Pp 150 Paris Masson & Cie, 1928

CONTRIBUTIONS TO THE STUDY OF TUBERCULOSIS By the Research Department, National Jewish Hospital, Denver No VIII Pp 510 Denver, 1927

## THROMBO-ANGIITIS OBLITERANS

### EXPERIMENTAL REPRODUCTION OF LESIONS \*

LEO BUEGER, M D

NEW YORK

In 1914, in a paper<sup>1</sup> entitled "Is Thrombo-Angiitis Obliterans an Infectious Disease?" my views regarding the nature of the pathologic process in this strange malady were definitely stated, and there, as in previous communications, the avenues of research through which proof of this contention could be expected, were clearly indicated. It was my belief, first, that the acutely inflamed veins and nodosities of thrombo-angiitis obliterans could furnish the material in which an infectious agent-virus or micro-organism might reside and be brought to light, second, that these foci might be utilized for the reproduction of the disease or, at least, of some of the acute lesions of the malady.

With this in mind, I conducted researches over a period of years (ten or more) with little success, both because the material was scant and because the methods used were faulty.

Cases of thrombo-angiitis obliterans, in the stage of migrating phlebitis, were seen from time to time, but some of the patients refused to allow the excision of the acutely inflamed veins, and others presented themselves at a time when the acuity of the process had already subsided.

Having failed to discover a micro-organism, I turned my attention to the reproduction of the "acute lesions."

It may be succinctly stated here that it is possible to reproduce lesions identical with those of acute thrombo-angiitis obliterans, acutely inflamed veins with military giant cell foci, in the superficial veins of the upper extremities of man, by transplantation of the coagulated contents of acutely affected veins when in the phase of migrating phlebitis.

I shall not, in this paper, delve deeply into a critical discussion of the conclusions that may be drawn from such experimentation, but shall content myself with a brief statement of my results in (1) simple ligation of the veins of the forearm or arm for control purposes, (2) implantation or inoculation of acute thrombo-angiitis obliterans coagulum into the lumen of ligated veins, (3) implantation of acute thrombo-angiitis obliterans coagulum against the walls of ligated veins in man and (4) implantation (as in 3) in monkeys.

\* Submitted for publication, Oct 3, 1928

1 Buerger L. Surg Gynec Obst 19 582 (Nov) 1914

## SIMPLE LIGATION

Having elsewhere emphasized the importance of stasis in the production of all thrombotic vascular conditions, and mindful of the importance of limiting the spread of suspected infectious material to the confines of the vein used for the experiment, I decided to isolate a vein, under procaine hydrochloride anesthesia, and doubly ligate it, including between the ligatures from one-half to an inch or more of its length, without disturbing its continuity. Whenever necessary, lateral tributaries were also

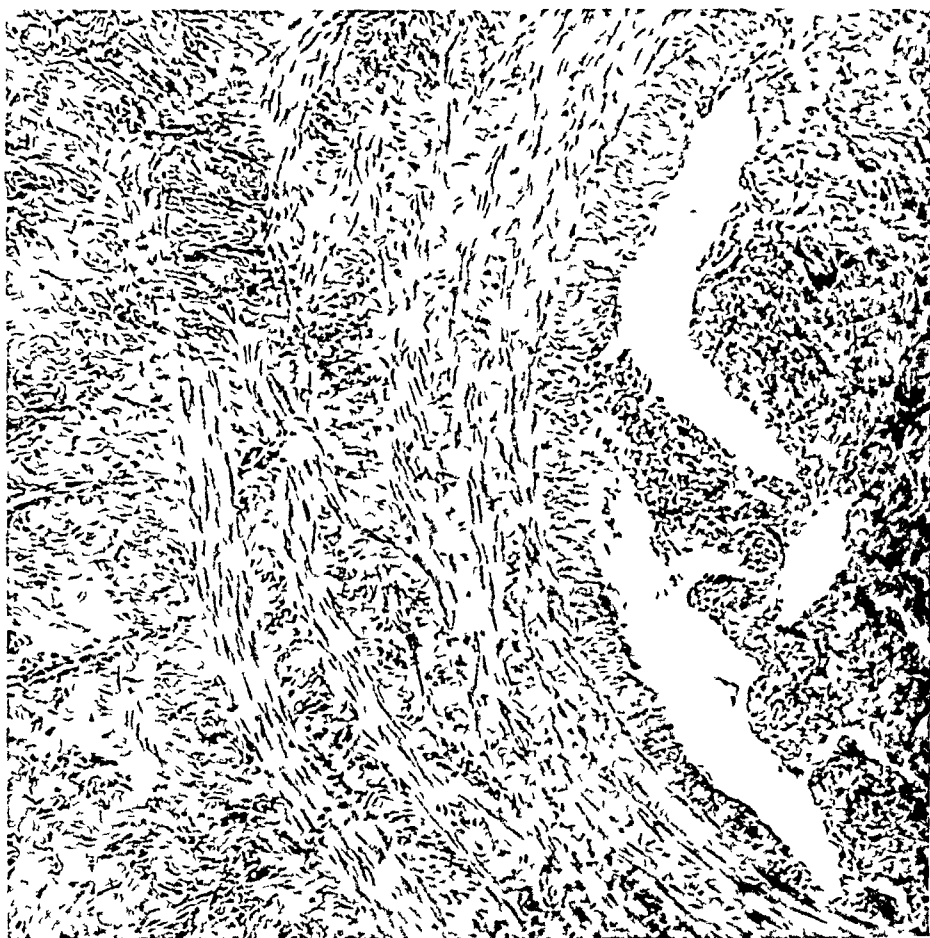


Fig 1—A part of the wall of a ligated vein of the forearm of a patient with thrombo-angitis obliterans. On the right may be seen the bland organization of a clot, in the middle, the wall of the vein without any sign of acute inflammation, and on the left, connective tissue about the vein.

tied off, and the lumen of the excluded vein was allowed to become somewhat overdistended with blood. In order that the vein might escape the influence of immediate contact with the repair tissue that would develop in and under the incision, the incision was placed about 1 cm to either side of the vein, and the isolation of this structure accomplished by a technic of undermining.

These experiments were conducted in (a) persons without vascular disease, (b) persons with thrombo-angitis obliterans and (c) persons

with moderately pronounced arteriosclerosis, a vein of the forearm being employed in each case

After from nine to twelve days, the veins were excised under local anesthesia, found thrombosed and examined microscopically



Fig 2—The acute inflammation of the wall and the inflammatory type of clot that are produced in a vein by paravascular implantations of clot from cases of thrombo-angitis obliterans

Bland thrombosis was regularly found in all instances. Whenever there was the slightest suspicion of infection of the wound, even if only

excessive reddening of it was encountered, the experiment was not included in the series

Figure 1 illustrates a part of the wall of a ligated vein of a patient with thrombo-angitis obliterans in the quiescent stages. On the right is a noninflammatory organizing thrombus adjoining a part of the vein wall. The latter does not show any sign of acute inflammation.

#### INOCULATION INTO THE LUMEN OF A VEIN

For about ten years I have had occasion from time to time to inoculate the veins of monkeys with emulsions of a coagulum taken from veins involved in the process of acute migrating phlebitis of the thrombo-



Fig. 3—A higher magnification of the section depicted in figure 2

angitis obliterans variety but without success. More recently (since 1926), I have repeated these experiments using human veins, with the full consent of those whose veins were employed, precautions having been taken as follows: first, the vein was tied off centrally and distally, second, all tributaries were also ligated, and, third (to date), only persons who had had thrombo-angitis obliterans many years before, but in whom symptoms were quiescent, were inoculated.

The technic was briefly this. As soon as a person with acutely migrating phlebitis of the thrombo-angitis obliterans variety presented himself, presumably less than a week after the onset of the lesion, his consent was obtained for the removal of a portion of an acutely inflamed and thrombosed vein. As much material as possible was removed. The excised vein was opened longitudinally, its clot lifted out

and placed in a sterile watch-glass containing a few drops of saline solution. With a sharp knife, the inner wall of the vein was also scraped, and whatever adhered to the knife was mixed into the clot as the latter was being broken up in the watch-glass. With the tissue suspension made as fine as possible, this mixture was aspirated into a small syringe. The patient into whose vein this material was to



Fig 4—A military focus with giant cell is to be seen above and the wall of the vein at the bottom of the picture, this is taken from another case in which lesions typical of thrombo-angitis obliterans were reproduced

be inoculated had been made ready on another table. Inoculation into the ligated vein, after it was moderately filled with blood, was accomplished by an oblique insertion of the needle through the wall of the vein and into its lumen.

All these experiments were failures. When the veins were excised from seven to twelve days later, a sanious mixture was found to be the vascular content.



Fig 5—Another section from the case illustrated in figure 4, showing several giant cells

#### IMPLANTATION OF THE COAGULUM ITSELF IN THE HUMAN VEIN

It became evident that the intravascular introduction of the suspected infectious material, because of its failure to permit of thrombosis, alone,



if for no other reason, must be substituted by a procedure that would not interfere with the clotting process. Therefore the following method was devised



Fig 6—A low magnification of a section from the forearm and vein in another case in which lesions of acute thrombo-angiitis obliterans were reproduced

Fresh material was sought and removed, as before, in aseptic fashion, but the clot was placed in a dry watch-glass or Petri dish, the scrapings from the intima remaining on the knife blade

With the vein to be inoculated, isolated and ligated as in previous experiments, and the incision placed at least 1 cm. on either side and parallel to the course of the vein, the material was introduced partly underneath, partly on the side or over

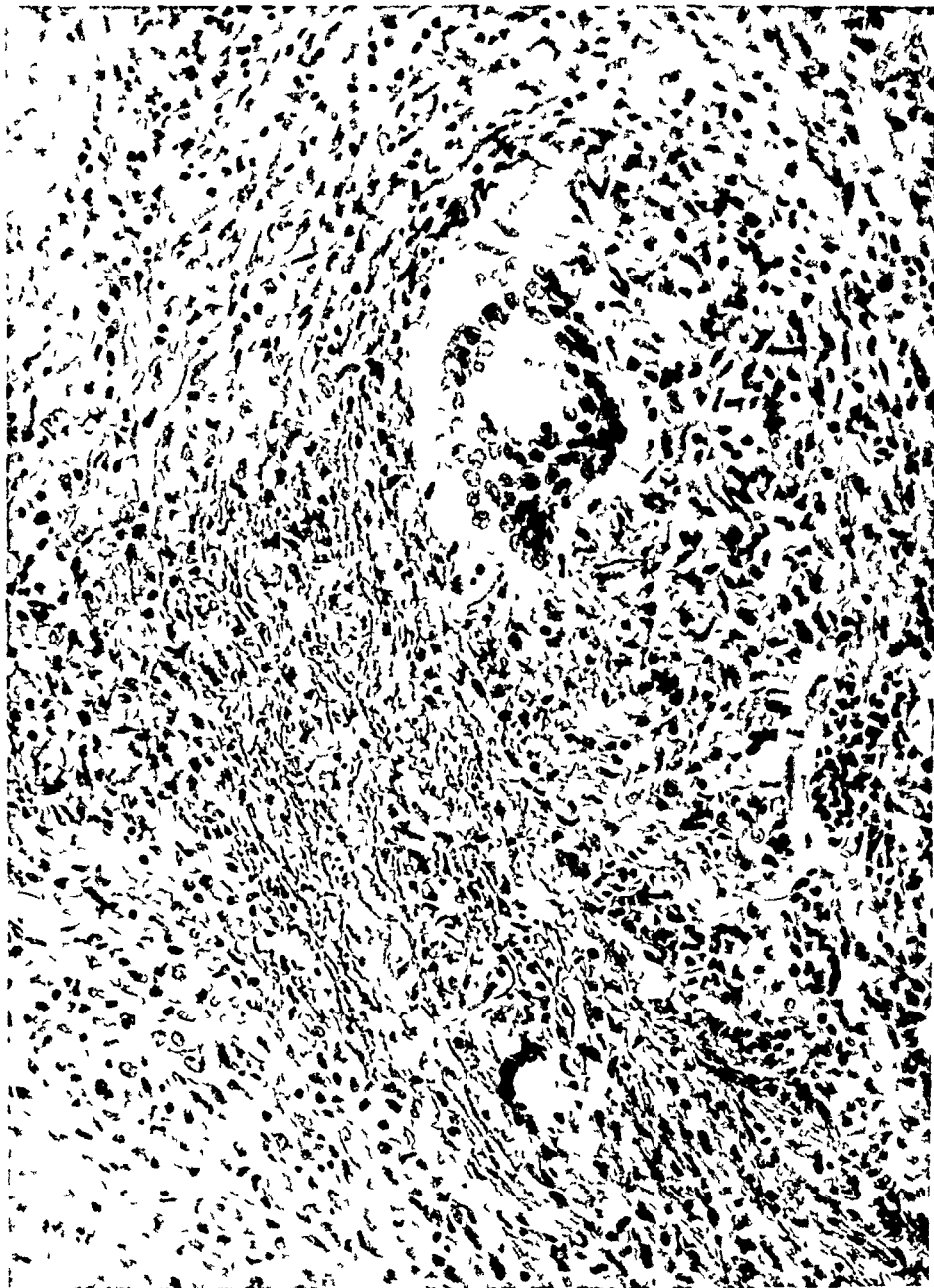


Fig 7—A high magnification of a portion of the same section shown in figure 6, presenting the same large giant cell referred to in the legend for figure 4. The wall of the vein is diffusely inflamed and the obturating clot contains a large giant cell.

the vein, and the smear of scrapings on the knife blade rubbed on the adventitia, which was sometimes lightly scraped or traumatized with the blade.

The skin was then sutured, great care being exercised that in this procedure such pressure was not exerted as might displace the fragments of the coagulum from their contact with the vein itself. Catgut other than that required for the

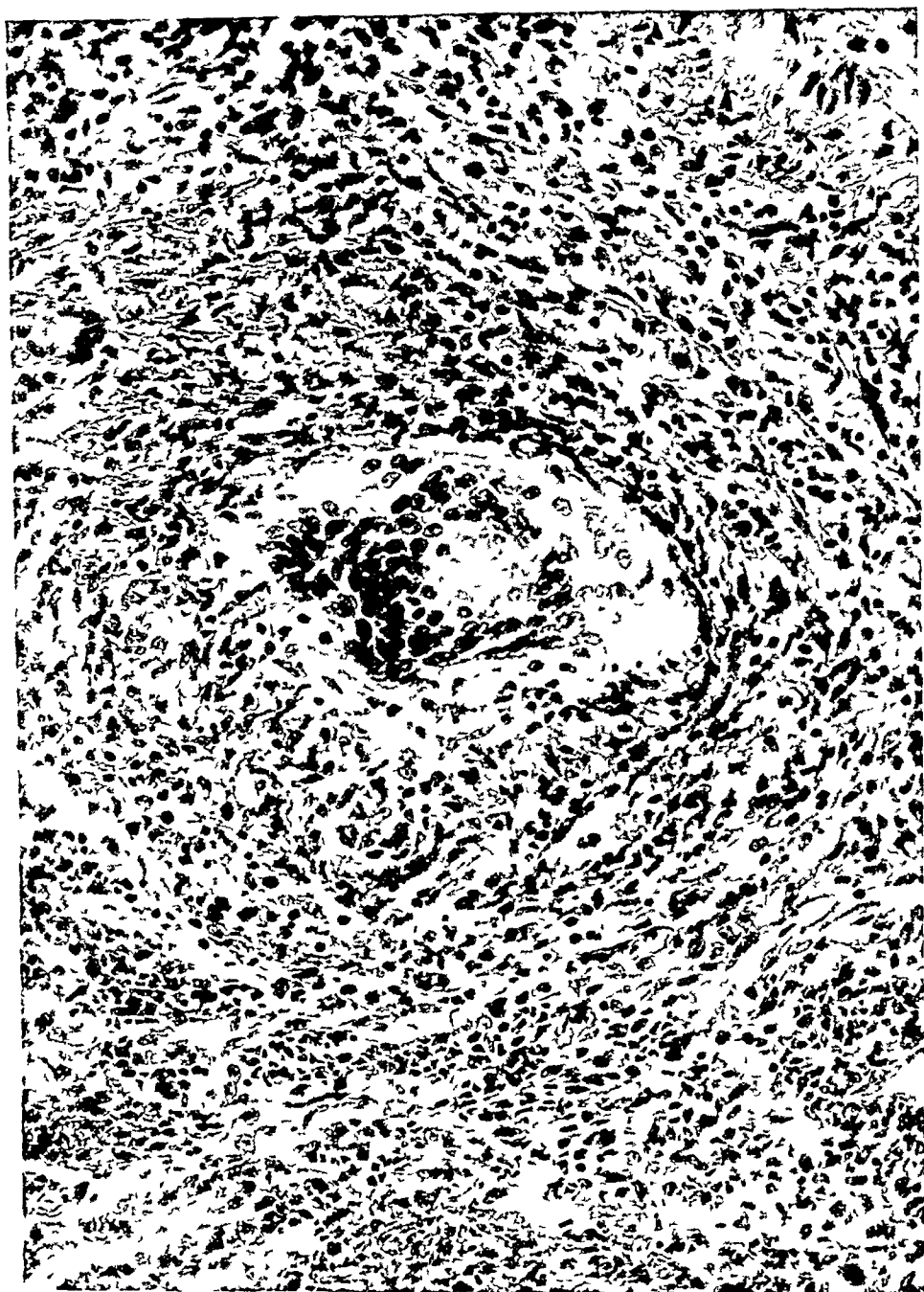


Fig 8—A high magnification of another portion of the section shown in figure 6, presenting the same large giant cell referred to in the legends for figures 4 and 6. The wall of the vein is diffusely inflamed and the obturating clot contains a large giant cell.

ligation of the vein was not employed, and filaments of gauze were not left in the wound lest they should act as foreign bodies around which confusing foreign-body giant cells might develop.

In all cases ligations without the implantations were carried out, as controls

The usual evidences of a mild nonpurulent phlebitis developed in at least four of eight cases. In two of the eight cases, a slight infection of the wound necessitated the rejection of the experiments, in two others, thrombosis occurred without any evidence of inflammation.

*Microscopic Examination*—In a thrombosed vein excised from nine to twelve days after the implantation, lesions practically identical with those of acute thrombo-angitis obliterans were found, namely, a diffuse polymorphonuclear infiltration of the wall of the vein and a clot containing typical miliary giant cell foci. The lesions in one case were particularly pronounced in a part of the wall of the vein, although polymorphonuclear invasion elsewhere was noteworthy (figs 2 and 3). The clot showed rare giant cells but inflammatory foci especially marked in the vicinity of the most intense mural changes.

In another case, a typical miliary giant cell focus was seen shown in the upper part of figure 4, with the inflamed wall of the vein below and near the margin of the picture.

A section taken from the same vein at another level is depicted in figure 5, in which the giant cell foci of the clot are more strikingly represented.

In still another experiment, there was reproduced a picture almost the counterpart of that which has been regarded as characteristic of acute thrombo-angitis obliterans (fig 6). Higher magnification in figures 7 and 8 shows details that are conceded by most pathologists to be pathognomonic of the disease in question.

#### SIMILAR EXPERIMENTS IN MONKEYS

In two experiments in monkeys I failed to produce other than bland thrombosis, a fact which would suggest that these animals may be immune. Other types of monkeys will be employed as soon as material becomes available.

#### CONCLUSION

The paravascular implantation of clot from cases of acute thrombo-angitis obliterans was followed by the development of typical lesions in the apparently healthy ligated veins of the inoculated person.

# ALLERGIC REACTIONS OF THE RABBIT'S INTESTINE DURING ANAPHYLACTIC SHOCK AS RECORDED CINEMATOGRAPHICALLY \*

E E ECKER, PH D

AND

M S BISKIND, M A

CLLVELAND

Since the fundamental paper by W H Schultz <sup>1</sup> on the reaction of the smooth muscle of the guinea-pig sensitized with horse serum and the subsequent studies by Auer and Lewis,<sup>2</sup> Dale,<sup>3</sup> Weil,<sup>4</sup> Coca,<sup>5</sup> Manwaring and Kusama,<sup>6</sup> Koessler, Lewis, and Walker <sup>7</sup> and others, it is now generally accepted as established that the isolated sensitized, non-striated muscle tissue will give strong contractions when brought into contact with the specific antigen. However, so far as we know, little, if any, work has been done on the response of the intestine of a sensitized animal in situ. The reaction of nonstriated muscle being so general and so vigorous, it was thought of interest to observe the change in physiologic response of the intact intestine of the rabbit.

## METHOD

Ten rabbits were sensitized to horse serum. Each of the animals received four injections of 5 cc of horse serum subcutaneously at intervals of from four to five days. Following the last injection, a period of from twelve to fourteen days was allowed to elapse before the toxic dose was given (intravenously). Two normal rabbits were used as controls.

For the observation of the intestinal reactions, the following method elaborated by us<sup>8</sup> was used. The spinal cord was severed in the lower thoracic region under ether anesthesia. Following the animal's recovery from the effects of the ether, a laparotomy was performed on it in the now insensitive ventral abdominal wall. By means of a special trough with its supports, a leak-proof

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\* Submitted for publication, Sept 26, 1928

From the Departments of Pathology and Pharmacology of the School of Medicine of Western Reserve University

1 Schultz J Pharmacol & Exper Therap **1** 549, 1909

2 Auer, J, and Lewis, P A Acute Anaphylactic Death in Guinea-Pigs, J A M **53** 458 (Aug 7) 1909

3 Dale J Pharmacol & Exper Therap **4** 167, 1912

4 Weil J M Research **30** 299, 1914

5 Coca J Immunol **4** 219, 1919

6 Manwaring and Kusama Abstr Bact Proc **1** 33, 1917

7 Koessler, K K Lewis, J H, and Walker, J A Pharmacodynamic Actions of Bacterial Poisons, Arch Int Med **39** 188 (Feb) 1927

8 Ecker and Biskind Arch Path, to be published

pouch was formed of the abdominal cavity, which was then filled with liquid petrolatum at a temperature of 38.5 C. For lighting and for maintaining a constant temperature, we used a 15 ampere direct current carbon-arc lamp with a single condensing lens, which rendered the light beam approximately parallel. This beam was reflected from a mirror into the trough. Motion pictures were taken with a 16 mm. Bell and Howell camera.

To produce the shock, intravenous injections of varying doses of horse serum were given as recorded in the accompanying table.

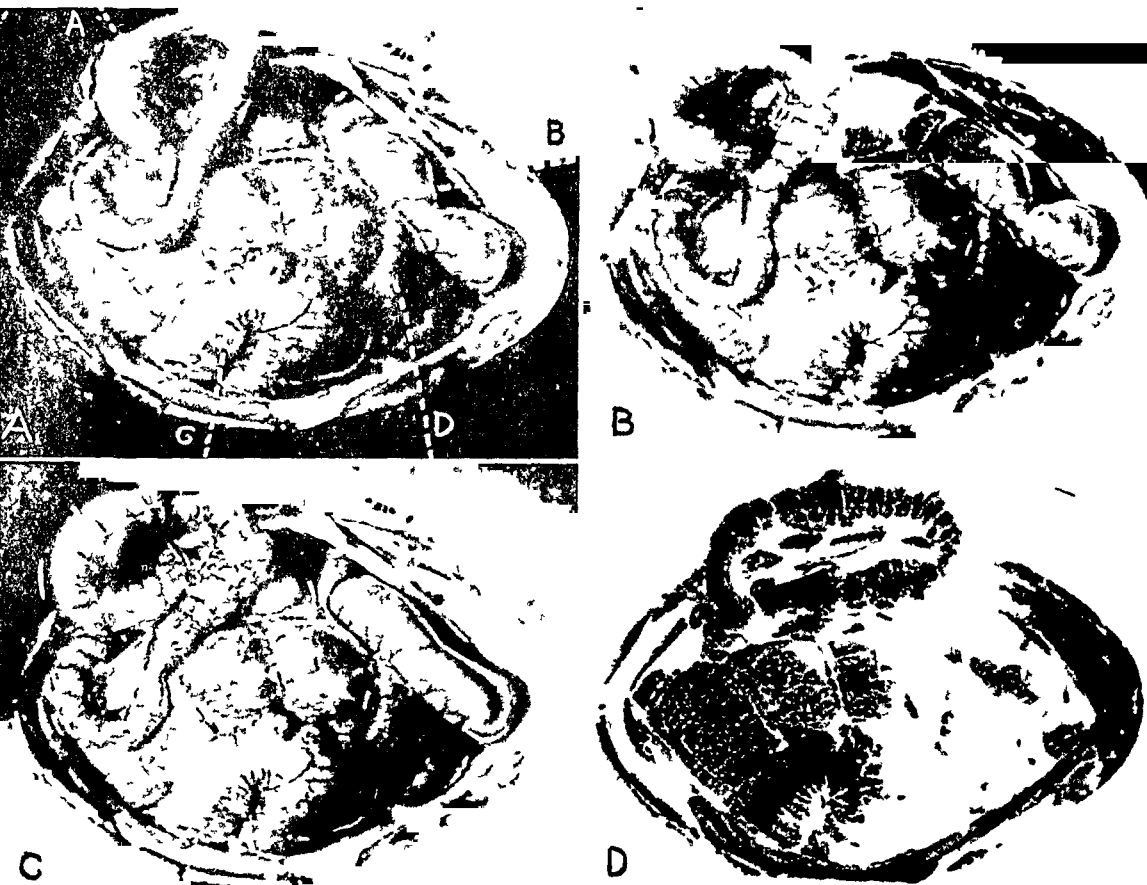


Fig. 1—Enlargements from a 16 mm. motion picture film of the intestinal pouch of rabbit 2 showing (A) an incomplete peristaltic rush, and (B, C and D) irregular spastic constrictions in the small intestine and a high tone of the cecum. Note the propulsion in the lower colon. In A, a indicates the small intestine, b, the lower colon, c, the upper colon, d, the cecum.

#### EXPERIMENTAL RESULTS

All ten sensitized animals reacted to the injections of the doses of horse serum by increases in respiratory rates. Seven exhibited definite intestinal reactions. The two nonsensitized animals used as controls did not show any increases in respiratory rates or any intestinal excitation on the injections of the horse serum. There was no regularity in the doses required to produce the intestinal responses, in the intervals

following the injections before the reactions occurred, in the parts of the intestines that reacted or in the types and degrees of severity of the contractions. Two animals showed irregular spastic contractions and incomplete peristaltic rushes (*Rollbewegungen*) in the small intestine (fig 1), one animal showed peristaltic rushes in the cecum (a rather rare phenomenon in the rabbit) and in the lower colon, together with local spasms in the small intestine (fig 2), two animals showed peristalsis in the cecum only, and two animals exhibited a moderate reactivity of the small and large intestines. Three rabbits did not show definite intestinal excitation. From two to seven consecutive shock doses were given to each animal, the one receiving the seven doses (in

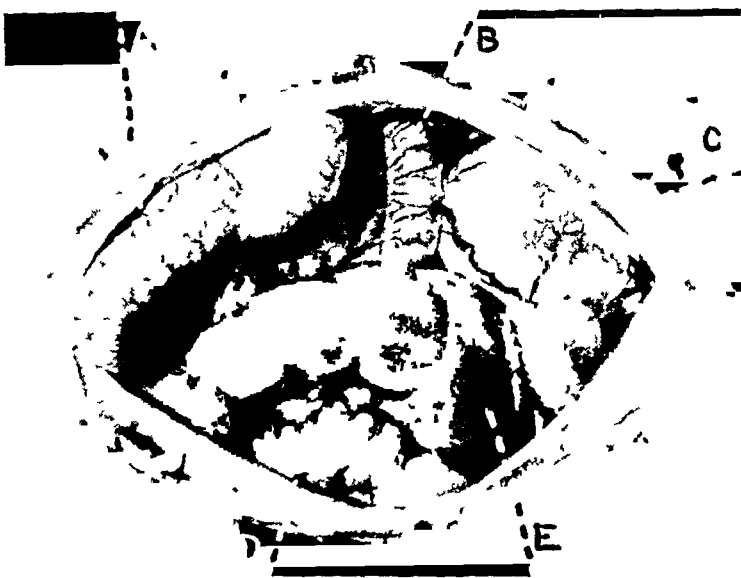


Fig 2—Enlargement from a motion picture film of the intestinal pouch of rabbit 7, taken during a peristaltic rush in the cecum. Note the prominent haustra in the upper colon and the high circular tone in the lower colon. Note also the distended bladder. A indicates the small intestine, B, the lower colon, C, the bladder, D, the upper colon, and E, the cecum.

a period of thirty-four minutes) reacted at each injection until the last. Other animals showed a similar response. In those animals in which the uterus was exposed, the horns were in a state of tonic contraction throughout the reaction.

That these results are of clinical significance in cases of allergy is evidenced by the following case, which came to our attention through the courtesy of Dr Milton B. Cohen.

A white woman, aged 30, had had hay fever for ten years. For three successive years, she had had preseasonal courses of injections of an extract of grass pollen and had thus obtained marked relief from her symptoms. In the fourth year, following the subcutaneous injection of 0.2 cc of a 1:1000 dilution of an extract of timothy pollen (1 gm of timothy pollen in 20 cc of a solu-

# Summary of the Allergic Effects on the Rabbit Intestine of Experimental Anaphylactic Shock

Ex- peri- ment	Weight, Gm	Time of the Severing of Spinal Cord	Time of the Lapar- otomy	Dose of Horse Serum, Cc	Time of the Injec- tion	Reactions	Summary of Intestinal Reactions
1 ♂	2 300	10 50	11 30	5	11 56	Marked increase in respira- tory rate immediately	No definite excitation
				5	12 00	No further reaction no definite intestinal excita- tion	
2 ♂	2,100	10 33	12 20	5	12 37½	At 12 38, spastic contrac- tions in some loops of small intestine and incom- plete peristaltic rushes in others, distinct increase in respiratory rate	Spastic constric- tions and incomplete peristaltic rushes in small in- testine
				,	12 50	During injection, same re- sponse as previously to 12 53	
				5	1 00	Same response	
3 ♂	2,000	9 25	10 00	5	10 20	At 10 30½ respiratory rate increased, slightly in- creased pendulum move- ments in small intestine	No definite excitation
				5	10 35	Cyanosis, strong contrac- tions of bladder, at 10 40, death	
4 ♀	2,150	9 27	10 45	5	11 02	Pendulum movements be- ginning in small intestine immediately at 11 02½ rapid respiration, at 11 04 cyanosis, uterus white and spastic, defecation, at 11 05 circular contraction in colon at 11 06 marked hour glass constriction of bladder lasting 3 minutes	Moderate increase in tone and reactivity of both circular and longi- tudinal muscula- ture
				2	11 10	Further immediate increase in respiratory rate at 11 11 considerable increase in circular tone of intes- tine at 11 13, circular spasm in colon	
				2	11 14	At 11 17 ileum spastic	
				2	11 19	Respiratory rate again in- creased, defecation, at 11 21, more defecation	
				2	11 22	More defecation, increased pendulum movement in small intestine	
				5	11 27	More defecation, at 11 29 respiration rapid and labored, at 11 30 uterus still spastic at 11 42 in- testine practically normal	
5 ♂	2,050	9 30	11 50	5	12 08	Respiratory rate moder- ately increased	No definite excitation
				5	12 12		
				5	12 14	Respiratory rate again in- creased, somewhat irregu- lar, slowed to normal in 1 minute	
				5	12 15		
6 ♀	2 280	9 19	10 15	5	10 27	Respiratory rate increased immediately at 10 29 pendulum movement starts in small intestine, at 10 31, respiratory rate extremely rapid	Strong local spasms and incom- plete peris- taltic rushes in small in- testine
				2	10 35	Pendulum movement marked in 1 minute	
				3	10 40	Respiratory rate further increased	
				2	10 52	At 10 55, strong local spasms and incomplete peristaltic rushes in sev- eral loops of small in- testine	
				2	10 58	More spasms and rushes immediately	
				1	10 59	More spasms and rushes immediately	
				1	11 01	No further reaction	



*Summary of the Allergic Effects on the Rabbit Intestine of Experimental  
Anaphylactic Shock—Continued*

Ex- peri- ment	Weight, Gm	Time of the Severing of Spinal Cord	Time of the Lapar- otomy	Dose of Horse Serum, Cc	Time of the Injec- tion	Reactions	Summary of Intestinal Reactions
7 ♂	2,450	9 20	11 15	5 5	11 26 11 26½	Increased respiratory rate peristaltic rushes in cecum and lower colon, and local spasms in small intestine, at 11 30, another rush in lower colon	Peristaltic rushes in cecum and lower colon, local spasms in small in- testine
				2 3	11 31 11 31½	Respiratory rate further in- creased, at 11 37, defeca- tion	
				2 2	11 41 11 43	Reaction in colon More defecation	
8 ♀	2,040	9 24	11 50	10	12 03	Immediate and marked in- crease in respiratory rate at 12 04, pendulum move- ment, at 12 05, peristalsis in cecum, pendulum move- ment in ileum	Peristalsis in cecum
				2	12 08	Respiration slow and shal- low heart rate slow, be- ginning contractions of bladder, at 12 10, peristal- sis in cecum, at 12 13 death	
9 ♀	1,920	9 26	12 20	10	12 27	At 12 29, peristalsis in cecum, pendulum move- ments in small intestine defecation, at 12 30, heart rate slow, no increase in respiratory rate	Peristalsis in cecum
				5	12 33	At 12 35, uterus extremely spastic and coiled up, con- siderable defecation, at 12 37, slight increase in respiratory rate	
10 ♀	1 800	9 30	12 45	8 5	12 51 1 05	At 12 55 rapid respiration Severe respiratory reaction lasting about 30 seconds at 1 08, pendulum move- ment more marked, uterus coiled up	Mild reac- tion of circular muscu- lature
				5	1 10	Severe respiratory reaction lasting longer than previ- ously, at 1 10½, middle colon spastic and longi- tudinally striated	
				2 5	1 14	At 1 16, constrictions of upper gut, at 1 22, defeca- tion, at 1 26 uterus a thin cord, at 1 27, propulsion in lower colon	
11 Control ♀	2,600	2 45	3 30	10 5	3 37 3 47	No reaction Mild circular contractions in one loop of small intes- tine	No definite excitation
				5	3 52	Pendulum movement in one loop of small intestine	
12 ♂ Control	2,450	2 50	4 05	10	4 15	No definite excitation of intestine to 4 40	No definite excitation

tion containing glycerol 66 per cent, and Coca's fluid 34 per cent) a severe and unusual reaction occurred within ten minutes. The usual respiratory and skin signs were mild, but there was marked abdominal pain, with nausea, projectile vomiting and a desire to defecate. Examination of the abdomen revealed visible peristalsis. Two injections of epinephrine each 0.4 cc of 1:1,000, and one of morphine sulphate ¼ grain (0.016 Gm) and atropine sulphate 1/150 grain (0.0019 Gm), were required to control the reaction. This lasted ninety minutes, and was followed by the passage of mucoid stools.

## SUMMARY

Direct observation and cinematographs of the rabbit intestine during anaphylactic shock showed irregular spastic contractions and incomplete peristaltic rushes in the small intestine and peristaltic rushes in the cecum and the lower colon. In some animals, the reactions occurred on successive injections of the homologous protein. Two nonsensitized animals used as controls did not show excitation of the intestine following the injection of the protein. The uterine horns of the rabbits were also observed, and were found to be in a state of tonic contraction during the reaction. One clinical case of marked intestinal reaction during allergy is reported.

# RADIOACTIVE SUBSTANCES IN A BODY FIVE YEARS AFTER DEATH\*

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The literature dealing with the effects of radioactive substances in the human body is scanty. Martland,<sup>1</sup> in 1925, was the first to refer to it in American literature. He showed that a bombardment by certain radioactive substances resulted in necrosis of bone and a terminal aplastic anemia. Reports concerning the danger of the ingestion or injection of radium are likewise few in number. Plesch and Larczag<sup>2</sup> showed that thorium X brings about a cumulative action in the body. A fatal case of poisoning with thorium X was reported by Bickel<sup>3</sup> in 1912. In 1914, Gudzent and Halberstaedter<sup>4</sup> noted the danger of radioactive substances in certain industrial pursuits. Their article dealt with persons who handled radium, and constituted a treatise on its dangers, pointing out that an improper handling of it may result in local skin lesions and changes in the blood.

## REPORT OF A CASE

In the case here recorded, the body was exhumed five years after interment for the purpose of obtaining evidence in connection with the death of the girl and the illness of several others who had been

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\* From the Department of Pathology, Bellevue Hospital, and the Department of Chemistry, Washington Square College, New York University

1 Martland, H S, Conlon, Philip, and Knep, J P. Unrecognized Dangers in Use and Handling of Radioactive Substances. With Especial Reference to Storage of Insoluble Products of Radium and Mesothorium in Reticulo-Endothelial System, J A M A 85 1769 (Dec 5) 1925

2 Plesch and Larczag. Handbuch der Radium Biologie und Therapie, Berlin, Julius Springer, 1910

3 Bickel. Berl klin Wchnschr 49 1322, 1912

4 Gudzent, F, and Halberstaedter, L. Deutsche med Wchnschr 40 633, 1914

employed at painting watch dials with luminous paint, the latter containing radioactive substances

*History*—A M, an unmarried girl, was born in the United States on Dec 21, 1897, of Italian parentage. The family history was negative, except that two sisters who worked in the same plant developed similar symptoms. The patient had been entirely well all her life except for minor illnesses. From November, 1917, to September, 1921, she was employed in a factory, painting watch dials with a mixture containing small amounts of radium and mesothorium, in the process of painting the watch dials, she "pointed" the brush between her teeth. In October, 1921, she had trouble with the teeth and complained of pains in various parts of the body, she became pale and lost some weight. At that time, she consulted a dentist who treated her teeth. The vague aches and pains, particularly pains in the joints, continued, and in March, 1922, she consulted a physician, who made a diagnosis of rheumatism and administered acetylsalicylic acid. A Wassermann test in January, 1922, was reported as negative. In June, 1922, another Wassermann test was reported to have been made with a 3 plus result. On the basis of this, a diagnosis of syphilis was made, and the patient was given seven intravenous injections of neoarsphenamine. By this time, she had developed necrosis of the lower jaw to such an extent as to require its almost complete removal. She became progressively worse and developed marked anemia. Records of blood counts taken at that time are not, however, available. Toward the close of her illness, she revealed a hemorrhagic tendency, bleeding frequently from the jaw, although purpuric spots were not noted. Death occurred on Sept 12, 1922. The death certificate was signed "ulcerative stomatitis," and syphilis was given as a contributory cause.

*Autopsy*—An autopsy was performed on Oct 15, 1927. The surface of the body was fairly well carbonized, the body had been embalmed in the right brachial artery. The lower jaw was entirely missing, except for the coronoid process on the left side, which was taken as a specimen. This specimen was necrotic and brittle. Both upper jaw bones were removed in several pieces and taken as specimens. Necrotic foci were present along some of the alveolar processes. The left side of the face and the left side of the upper lip, which were well preserved, were also taken as specimens. The subcutaneous fat was decomposed, giving a distinct odor of butyric acid and having a soapy consistency. Lesions in the heart and the aorta could not be seen with the naked eye. The valves and the coronary vessels were smooth, a foramen was not present. The lungs were collapsed, but otherwise were well preserved, the bronchi were pale and somewhat granular. The liver weighed approximately 600 Gm, on cross section, it was somewhat fatty and emitted a rancid odor. The gallbladder was collapsed, but did not show any gross changes. The spleen was small, soft and mushy, but otherwise did not show gross lesions. The kidneys were small and were embedded in a small amount of rancid fat, on cross section, they were found to be dark green, the markings were not distinct, and there was considerable postmortem change. The cortex of the suprarenal gland was well preserved, the medulla was soft and mushy, and was discolored greenish black. The bladder was collapsed. The uterus was small and virginal. The ovaries were small and did not show gross changes. The stomach was collapsed, it did not show gross changes. The intestines were collapsed, they contained a small amount of fecal residue. The esophagus was smooth and without gross changes. The thyroid was small and somewhat soft, but did not present other changes. The thymus was not present. The skull was sawed through the median line and both halves

of the brain were taken, the brain was firm and well preserved, and changes were not apparent to the naked eye. All the bones of the skull were removed for chemical analysis, as were also the second, third, fourth, fifth and seventh cervical vertebrae, portions of the fifth, sixth, seventh, eighth and ninth ribs on the right, both feet, the right femur, tibia and fibula and the left femur. The bones, after except the postmortem degeneration. Smears and sections of the bone-marrow did not show any recognizable cellular structures.

Microscopic examination of the viscera did not show any histologic lesions except the postmortem degeneration. Smears and sections of the bone-marrow did not show any recognizable cellular structures.

#### PHYSICOCHEMICAL WORK THE ANALYSIS

*Preparation of the Bone Samples*—Adhering tissue was removed as completely as possible from the bones by scraping them with a knife. The bones were then boiled for from two to three hours in a sodium

TABLE 1—*Weights of Bones Before and After Drying, and After Reduction to Ashes in Preparation for Their Use in the Quantitative Estimation of Radioactive Substances*

Bones	Weight Before Drying, Gm	Weight After Drying, Gm	Moisture, Per Cent	Ash Obtained, Gm	Ash, Per Cent
Upper jaw bone	4.34	3.995	8.0	1.820	41.8
Lower jaw bone	2.64	2.434	7.8	1.108	42.0
Vertebrae	4.46	3.705	16.9	2.390	53.5
Tibia	12.47	10.600	15.0	6.705	53.7
Femur (piece)	25.90	21.750	16.0	13.760	53.1
Femur (piece)	11.44	9.950	13.0	5.610	49.1
Skull (piece)	8.91	7.350	17.5	4.770	53.5
Femur (piece)	46.47	39.500	15.0	25.130	54.1

carbonate solution to loosen and soften adhering tissue, they were then thoroughly washed. Next, they were dried at a temperature ranging between 100 and 105 C. The long bones (tibia and femur) were sawed into lengths of from 1½ to 3 inches (from 2.5 to 7.6 cm). The following bones were thus prepared: skull bone, upper jaw, piece of lower jaw, vertebrae, femur, tibia, metacarpals and phalanges.

*Preparation of Bone and Tissue Ashes*—Bones as listed in table 1 were scraped and cleaned free of all muscle and fat tissue and wiped as dry as possible. They were weighed, then dried at from 95 to 100 C to constant weight and finally ignited to a grayish-white ash and again weighed. The results are recorded in table 1. These ashes were used for the quantitative estimation of radium.

Weighed portions of tissue, as listed in table 2, were ground up, dried and ignited to a grayish-white ash. The ash so obtained was weighed. The values are recorded in table 2. The ash from the organs mentioned in table 2 was used in the electroscopic and photographic experiments.

*Presence of Radioactive Substance Determined with the Lind Electroscope*—The normal leak was first determined by several trials. It was found to be as an average of 3,000 seconds for 10 divisions on the scale. The bone ash and the tissue ash were then successively introduced into the lower chamber of the electroscope and the leak determined. These leaks were always determined with the leaf between

TABLE 2—*Weights of Organs Before and After Reduction to Ashes in Preparation for Their Use in Electrosopic and Photographic Experiments to Determine Presence of Radioactive Substances*

Organs	Total Weight of Organ, Gm	Weight of Organ Ashed, Gm	Ash Obtained, Gm	Per Cent Ash	Calculated Ash from Whole Organ, Gm
Liver	375	2.0	2.221	0.8	4.60
Lung	212	.92	0.851	0.92	1.95
Spleen	55	.26	0.246	0.95	0.52
Brun	485	122	0.590	0.49	2.35

TABLE 3—*The Leaks Obtained for the Bone Ash and the Tissue Ash in an Experiment Determining Quantitatively the Presence of Radioactive Substances*

Material Tested	Gm	Divisions	Seconds
Normal leak	Control	10	3,000
Femur (head)	21.75	10	25
Femur (shaft)	9.95	10	78
Skull bone	7.35	10	153
Vertebrae	3.70	10	45
Femur (shaft)	11.52	10	61
Jaw (upper)	9.55	10	47
Jaw (lower)	5.62	10	66
Liver (ash)	2.22	10	310
Spleen (ash)	0.24	10	171
Brun (ash)	0.59	10	104
Lung (ash)	0.85	10	65
Femur (bone ash)	1.00	10	192

TABLE 4—*The Leaks Obtained for the Bones and Tissue Ashes of Normal Persons*

Material Tested	Gm	Divisions	Seconds
Normal leak	Control	10	3,000
Jaw bone	12.50	10	2,980
Vertebra	5.15	10	2,890
Femur	22.95	10	2,910
Liver (ash)	3.50	10	2,930
Brun (ash)	0.95	10	3,010
Spleen (ash)	0.56	10	2,920

6 and 8 of the scale, making successive readings strictly comparable. The results are indicated in table 3. The figures show an enormous reduction in the leakage time, indicating that all the bones and all the tissue ashes examined, without exception, were strongly radioactive.

Bones and tissue ash of normal persons were then tested with results as shown in table 4. The values are practically the same as the natural leak, showing the absence of radioactivity.

The earth taken from around the coffin was dried and also tested, with results as recorded in table 5. These results do not indicate any appreciable radioactivity.

*Presence of Radioactive Substances Determined by Photographic Method*—All operations were performed in a dark room. A series of x-ray films were enwrapped in black photographic paper and sealed, to make them light proof. On these were placed various bones and tissue ash, also normal bones for controls. They were allowed to remain in this manner for ten days. If radioactive, the bones and the tissue ash would emit rays, and the beta and the gamma rays would penetrate the black paper and affect the photographic films. After ten days, the films were developed and printed. The results are shown in the accompanying photographs. Those on which normal bones were placed are not shown, because they did not show any impression.

TABLE 5—*The Leaks Obtained for Earth from Around the Coffin*

Material Tested	Gm	Divisions	Seconds
Normal leak	Control	10	3,000
Earth in box	50	10	2,660
Earth 1 foot below	50	10	2,540
Earth on top	50	10	2,650

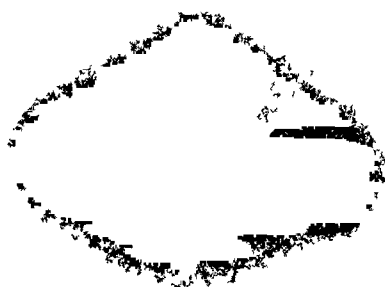
A few films were wrapped in sheet lead (size 0.3 mm), bones were placed on them and they were kept in a dark room. These did not show any effect after two weeks. They were then left standing for three months, at the end of which time a good picture was obtained. This impression was due solely to the gamma rays, as the alpha and the beta rays were completely screened off by the lead. This picture is also shown (part 4 of plate).

Every piece of bone, as well as every tissue ash that we examined, showed radioactivity by the photographic method.

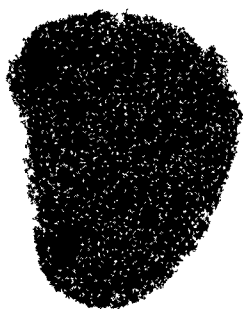
*Presence of Alpha, Beta and Gamma Rays Determined*—Radium emits three kinds of rays: alpha, beta and gamma rays. If a radioactive substance is placed in the chamber of the electroscope, the leak produced is due to the total effect of all three rays. If the radioactive substance is completely enclosed in sized paper, the alpha rays are withheld and the leak produced is due to the beta and the gamma rays only. If the radioactive substance is enclosed in a lead chamber, both the alpha and the beta rays are withheld and the leak produced is due to the gamma rays only. This experiment was tried with results as shown in table 6. It indicated that all three rays were coming from the bones.



1



2



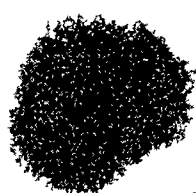
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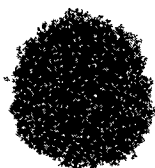
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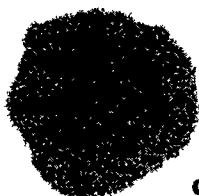
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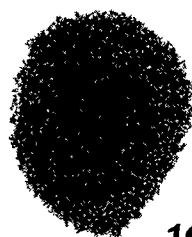
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10

Radium rays from various tissues of the body five years after death in a case of industrial contact with radium 1 piece of lower jaw, 2 vertebra, 3, femur, 4, femur through lead, 5 tibia 6, liver, 7 metacarpal bone 8, brain, 9 lung, and 10 spleen ash



*Determination of the Nature of the Active Deposit*—A sample of femur (1 Gm) was dissolved in strong hydrochloric acid. The emanation was plated off on a copper wire, suspended above the solution. The wire was charged negatively, 135 volts potential with respect to the solution. After thirty minutes, the wire was removed, placed in the charged electroscope and the leak determined. The change of the leakage rate was determined as a function of the time, thus giving a measure of the rate of decay of the deposit thus obtained. The values are indicated in table 7.

This experiment showed that the leakage time was shortest at the beginning, and then steadily increased, meaning that the deposit was

TABLE 6—*The Leaks Obtained for Bone (1) Without Shutting Off the Radioactivity, (2) with Alpha Rays Withheld and (3) with Alpha and Beta Rays Withheld*

Material Tested	Divisions	Seconds
Natural leak	10	3 000
One vertebra, as such	10	22 5
Same vertebra enclosed in paper	10	63
Same vertebra enclosed in lead	10	506

TABLE 7—*Results in Determination of the Nature of the Deposit of Radioactive Substance in the Bone*

Time at Which Readings Were Taken A. M.	Time for One Division, Seconds (Plating stopped)
10 00	
10 01	130 2
10 05	195 0
10 12	245 2
10 21	274 6
10 31	328 4
10 44	337 1
11 21	431 8
Normal leak this day	442 0

most active at the beginning. Radium emanation produces just such an effect. With mesothorium, the leakage time at first decreases and then, after from three and one-half to four hours, it gradually increases. The picture obtained from the emanation in this bone indicated that it was an emanation from radium.

#### QUANTITATIVE WORK

*Quantitative Calibration of Electroscope in Terms of One of Known Radium Content by Emanation Method*—The Lind electroscope was used for all the measurements in this investigation. It was calibrated by the emanation method, as follows:

A sample of carnotite ore weighing 1 Gm and containing 1.58 per cent uranium was placed in a 200 cc round bottom flask, covered with 100 cc of 1:1 nitric acid.

and saturated with barium nitrate and the flask content was boiled to expel all the emanation. With the content of the flask at boiling temperature, the flask was sealed and the emanation allowed to collect for a period of one week. After this time, the sealed flask was connected with a purifying train (to remove carbon dioxide, acid spray and moisture) and the emanation was driven over into a previously evacuated ionization chamber. The emanation was allowed to stand in the chamber for three hours before measurements were begun, in order to allow it to come to equilibrium with its surroundings. The electroscope head was then mounted on the ionization chamber and charged for fifteen minutes at 135 volts, and the rate of leak determined. The average of several determinations gave 14.4 seconds for 10 divisions leak. Since the natural leak of the instrument is 3,000 seconds per ten divisions, the latter is not of significance as a corrective factor.

Since the ore contained 1.58 per cent uranium, the amount of uranium present was  $1 \times 0.0158 = 0.0158$  Gm uranium.

The radium to uranium ratio—that is, the amount of radium element in equilibrium with 1 Gm of uranium—is accurately known and has the value

$$\text{Ra/U} = 3.33 \times 10^{-7}$$

It is known, however, that only 97 per cent of this amount gives off emanation, so that the corrected amount of radium equivalent to the aforementioned sample and measured as stated is

$$\text{Radium} = 0.0158 \times 3.33 \times 0.97 \times 10^{-7}$$

$$\text{Radium} = 5.06 \times 10^{-9} \text{ Gm}$$

This amount of radium, then, gives the observed leak of ten divisions in 14.4 seconds.

*Quantitative Determination of Radium on Several Tissue and Bone Ashes by the Emanation Method*—One gram samples of ash were treated exactly the same as was the carnotite ore in the calibration. The rate of leak was determined in each case. From the calibration just described, it was found that  $5.06 \times 10^{-9}$  Gm of radium causes ten divisions leak in 14.4 seconds. Hence, the radium content of this series was calculated by the following equation

$$\frac{14.4}{\text{Leak time for 10 div in sec}} \times \frac{1}{\text{Wt taken in Gm}} \times 5.06 \times 10^{-9} = \text{Gm Ra per Gm of ash}$$

Table 8 shows the radium content of the bone ashes and the tissue ashes as determined by this method.

Assuming a body weight of 100 pounds (45 Kg), 18.3 per cent of which was bone, the bone ash being 51 per cent of the bone proper, we found that the entire bone ash content in the body was 4,198.5 Gm. The total radium content in bones, liver, lungs, spleen and brain was, therefore, 48.4179 micrograms (table 9). It must be remembered, however, that this value for the radium content was from about 22 per cent of the entire body weight only.

## SUMMARY

A case is described in which radioactive substances were recovered from a human body five years after death

The bones (jaw, vertebrae, femur, tibia, skull, metacarpal and phalanges), and the liver, brain, lungs and spleen were tested for signs of radioactivity. Every portion of tissue and of bone tested gave photographic evidence of radioactivity. Every portion of tissue and of bone tested gave electroscopic evidence of radioactivity. All three rays (alpha, beta and gamma) were detected.

TABLE 8—*The Total Amount of Radioactivity in the Bone and Organ Tissues as Determined by the Emanation Method*

Bones and Tissues	Grams Radium per Gram of Bone Ash	Micrograms Radium per Gram of Bone Ash
Vertebrae	$2.12 \times 10^{-8}$	0.0212
Femur	$1.01 \times 10^{-8}$	0.0101
Upper jaw	$1.19 \times 10^{-8}$	0.0119
Skull	$0.37 \times 10^{-8}$	0.0037
Tibia	$0.63 \times 10^{-8}$	0.0063
Lower jaw	$1.58 \times 10^{-8}$	0.0158
Lungs	$2.76 \times 10^{-8}$	0.0276
Brain	$1.01 \times 10^{-8}$	0.0101
Spleen*	$1.03 \times 10^{-8}$	0.0103
Liver	$0.69 \times 10^{-8}$	0.0069

\* 250 mg. of spleen ash used

TABLE 9—*Estimation of the Total Radium Content of Bones and Organs Taken from Exhumed Body*

Tissues Used for Estimation	Weight of Ash from Entire Body, Gm	Average Radium Content per Gm in Micrograms	Total Radium Content in Micrograms
Bone	4,198.5	0.0115	48.282
Liver	4.6	0.0069	0.037
Lungs	1.95	0.0276	0.0538
Spleen	0.52	0.0103	0.0214
Brain	2.35	0.0101	0.0237
Total			48.4179

The nature of the emanation was found to be that of radium. Quantitative determination (by the emanation method) showed the presence of 48.282 micrograms of radium in the entire skeleton. The radium content was also estimated for the lungs, liver, spleen and brain. The total estimated radium content for entire bones, liver and lungs was 48.4179 micrograms.

## CONCLUSIONS

Radium salts that are absorbed find permanent lodgment in both the viscera and the bones, particularly the latter. The manner and course of its distribution cannot be stated with certainty, although there appears to be a predilection for lodgment in the bones. The bombardment of the bones by the radium rays causes increased brittleness and necrosis.

# OSTEOGENIC SARCOMA IN DIAL PAINTERS USING LUMINOUS PAINT \*

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Of some fifteen girls whose deaths were attributed to radium-mesothorium poisoning incurred while they were employed at painting watch dials with luminous paint, two were found to have osteogenic sarcoma of the bone.

The etiology, the general and the special symptomatology, the pathologic anatomy, the prognosis and the treatment in this new industrial hazard were first described by Martland and his associates in 1925 and 1926.<sup>1</sup>

Only a brief résumé of the observations on this disease is necessary in this paper.

The paint used consisted of crystalline phosphorescent zinc sulphide, ZnS (Sidot's blend), rendered luminous by the addition of extremely small amounts of radium, mesothorium and radiothorium. These radioactive substances were in the form of insoluble sulphates in the paint when it was used.

The mode of poisoning in these cases was by ingestion. Owing to a general habit among these workers of pointing their brushes in their mouths while painting the dials, they swallowed small amounts of the radioactive paint day after day. They were also exposed to radioactivity by absorption of the substance through the skin and by inhalation, especially of the dust of the luminous paint, but these portals of entry were not considered significant. The girls affected had swallowed the paint for periods of from one to four years or more.

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From the Pathologic Department of the City Hospital, Newark, N. J., and the office of the Chief Medical Examiner of Essex County, N. J.

Read before the New York Pathological Society at the New York Academy of Medicine, New York, March 8, 1928.

1 Martland, H. S., Conlon, Philip, and Knief, J. P. Some Unrecognized Dangers in the Use and Handling of Radioactive Substances (with Special Reference to the Storage of Insoluble Products of Radium, Mesothorium, etc., in the Reticulo-Endothelial System), *J. A. M. A.* **85** 1769 (Dec. 5) 1925. Martland, H. S. Microscopic Changes of Certain Anemias Due to Radioactivity, *Arch. Path.* **2** 465 (Oct.) 1926. Reitter, G. S., and Martland, H. S. Leukopenic Anemia of the Regenerative Type Due to Exposure to Radium and Mesothorium, *Am. J. Roentgenol.* **16** 161 (Aug.) 1926.

Most of the paint swallowed passed rapidly through the gastrointestinal tract and was eliminated. A small amount, however, was continually absorbed and eventually stored as insoluble sulphates of particulate or colloidal size in the main organs of the reticulo-endothelial system and, above all, in the bones. The exact mode of intestinal absorption is not clear. Whether the insoluble radioactive substance was picked up by wandering histiocytes of the intestine and taken into the thoracic duct, then to the blood and then to the storage organs, in which it was phagocytosed by the fixed histiocytes of the blood sinusoids, the Kupffer stellate cells of the liver and the splenic phagocytes, whether small quantities passed through the intestinal tract in a manner not understood, or whether the radioactive substances had some fixed position in the zinc sulphide molecule which allowed it to be absorbed with the zinc is unsettled at present. Perhaps the conceptions of absorption from the intestinal tract must be augmented and modified considerably. It should be recalled that the entrance into the body of insoluble matter of particulate size is thought to be easier by inhalation than by ingestion. For instance, in anthracosis, the foreign matter is readily picked up from the alveoli of the lungs by the phagocytic cells or histiocytes of the reticulo-endothelial system, and then by lymphatic drainage it is distributed over the entire lung and taken to the hilum nodes in enormous quantities. Anthracosis of the intestinal tract and its lymphatics is, on the other hand, unusual. The same anatomic pathways are seen in exogenous infection of the lung with human tubercle bacilli.

The deposits in the bones were generalized over the entire skeleton. One bone did not contain more radioactivity than another. A study of its minute distribution in the individual bones (which, on account of the extremely small amounts present, could be determined only by photographic methods) showed an irregular distribution in the bone and often a concentration in certain portions. The outer layers of the cortex seemed to be the final position of storage. Here it was frequently stored in large amounts and probably replaced calcium in these areas.

After final deposition in the bones, these deposits emitted their characteristic radiations day after day (every minute of the twenty-four hours), month after month, and year after year. As about 95 per cent of the radiation coming from these deposits was alpha and only 5 per cent beta and gamma, the blood-forming centers, owing to their proximity, were constantly bombarded by the alpha particle, exposing vital centers to a type of radiation never before known to have occurred in human beings.

The alpha particles are probably the most potent and destructive agent known to science. They consist of nuclei of helium atoms containing two positive charges ( $\text{He}^{++}$ ) ejected from the radioactive

substances with great force, attaining an initial velocity equal to from one twentieth to one twelfth that of light. Aside from the beta rays, which are negative electrons and much smaller, they represent the fastest space-occupying objects yet known. They collide with other atoms with terrific impact, usually jerking off a negative electron. The chemical changes resulting from this ionization are of the ordinary molecular character. Occasionally, the alpha particle may strike the atomic nucleus of lighter atoms, causing disruption with the liberation of a high velocity atom of hydrogen (H rays). Biologically, the alpha rays are much more destructive than either the beta or the gamma rays, the relation being 10,000 to 100 to 1, respectively. Therefore, radioactive elements in such small amounts that the beta and the gamma radiations are almost negligible still produce, through their alpha radiations, intense physiologic effects, if given by mouth or vein.

In addition, the preponderance of mesothorium in this paint is of great toxicologic importance for the reason that mesothorium in equilibrium with its radiothorium emits five alpha particles, whereas radium emits only four, also, the alpha particles of mesothorium and the products of its decay have a greater velocity and penetration than those of radium, and, therefore, are, chemophysically and physiologically, more active.

As a result of the continuous and constant radiation from the deposits on the blood-forming centers, especially of the deadly alpha rays, these centers in time became exhausted, and a leukopenic anemia, in most cases of the regenerative type, but occasionally of the aplastic or aregenerative type, developed. This anemia often proved fatal. Anemias previously recorded, due to external radiation, were all described as aplastic. This judgment was based almost entirely on clinical observations, unsupported by autopsy and histologic evidence these being, unfortunately, lacking in almost every case. The alpha particle never entered into the etiology to any extent, as the radiation was almost entirely penetrative and chiefly due to gamma rays.

Due to a continuous radiation from the deposits, a radiation osteitis often developed in these cases, similar to that seen in bones as a result of large doses of external irradiation. Because of the proximity of the mouth—the dirtiest part of the body—to the mandible and the maxillae, a superadded bacterial infection, usually by way of the teeth, resulted in extensive, intractable necrosis of the jaw, which, together with the anemia, formed the outstanding clinical features of the early fatal cases.

In the later cases (at the time of writing the patients are still alive), a sufficient period of time had elapsed after the exposure (from six to seven years) to allow the mesothorium, which formed some 70 per cent of the radioactivity, to diminish in quantity by its own natural,

uninfluenceable decay to below one-half its strength (67 years, half period) In the later cases, therefore, the patients seemed to be escaping the extensive necrosis of the jaw and the fatal leukopenic anemias of the regenerative type They showed, however, chronic crippling lesions of the bones the result of radiation osteitis, most marked in the bones that were subject to weight, pressure and trauma, such as the head of the femur and the acetabula, the spine, the scaphoid bone of the foot, etc The anemias were milder, and, if progressive, were more apt to be of the aplastic or aregenerative type, and to be characterized at autopsy by a bone marrow similar to that seen in chronic benzol poisoning

As regards the occurrence of sarcoma of the bone in these cases, unfortunately, in the first case, the clinical data are meager, and pathologic material is not now available In this case, the girl died in 1924 A clinical diagnosis of osteogenic sarcoma of the femur was made from the symptoms and the roentgenograms She was treated by deep roentgen therapy The presence of sarcoma, however, was never proved by operation or autopsy

In the second case, a diagnosis of osteogenic sarcoma of the scapula was made during life and proved at autopsy After a fall, in which the patient hurt her right shoulder, a sarcoma of the scapula developed to which, in addition to a severe anemia, she succumbed She never had severe necrosis of the jaw, but during life showed evidence of a radiation osteitis in the scaphoid bone of the right foot, in the heads of both humeri and in the glenoid cavities Her bones after death were radioactive, and it appears plausible that the sarcoma originated in a bone that previously had been the seat of a radiation osteitis

The incidence of two sarcomas of bone in fifteen cases of radium-mesothorium poisoning is too large to be passed over as due to coincidence Since this is the first time to our knowledge that sarcoma of the bone has been attributed to radiation, the case is of sufficient interest to be reported

#### REPORT OF CASE

*History*—A woman, aged 33, worked as a painter of dials eight years before her death When applying luminous material to watch dials, she was in the habit of pointing the brushes with her lips She had little trouble with her teeth and never had any extensive necrosis of the jaw Roentgenograms taken by a dentist in 1926 showed lesions, which we have interpreted as typical radiation osteitis, involving chiefly the alveolar portions of the mandible

In September, 1926, fourteen months before her death, she fell while working in a department store, injuring her right shoulder There was pain with limited motion, and she was later referred to the compensation department Roentgenograms showed a slight downward displacement of the head of the humerus She was operated on, but disease was not found in her shoulder The wound healed promptly without complications

In July, 1927, six months before her death, she still complained of pain in her right shoulder. She also had pain and localized tenderness over the scaphoid bone of her right foot. At this time, she was seen by one of us (H). An examination of the original roentgenograms demonstrated peculiar changes in the right humerus, the scapula and the scaphoid bone of the right foot. He concluded that the condition resembled a radiation osteitis similar to that seen in other painters of dials. It was then ascertained that she formerly had been a dial painter.

In September, 1927, three months before her death, roentgenograms for the first time showed a sarcoma of the right scapula, springing from its anterior and upper portion and an osteitis of the scaphoid bone of the right foot with fragmentation.



Fig 1—Roentgenogram of the right shoulder, taken five months before death. Evidence of a radiation osteitis may be noted in the head of the humerus, the acromion and the glenoid process.

In December, 1927, she returned to the hospital with her right upper extremity markedly swollen down to the hand. She had pain, which was constant and unrelieved by morphine. To lessen the pain, an operation was performed to relieve pressure on the main nerve trunks. Large masses of tumor tissue were removed. She died a few hours later. During life, tests were not made to prove the presence of radioactivity in her body, such as the examination of the expiratory air for the presence of emanation or an examination for the alpha particle by scintillation methods, or the use of the gamma electrometer for the demonstration of penetrative radiations coming from the body. The latter method, however, is of little use in these cases, on account of the extremely small amounts deposited in the bones.





Fig 2—Roentgenogram of the right shoulder, taken two months before death. An extensive, rapidly growing osteogenic chondrosarcoma may be noted springing from the anterior surface of the scapula and the glenoid process.

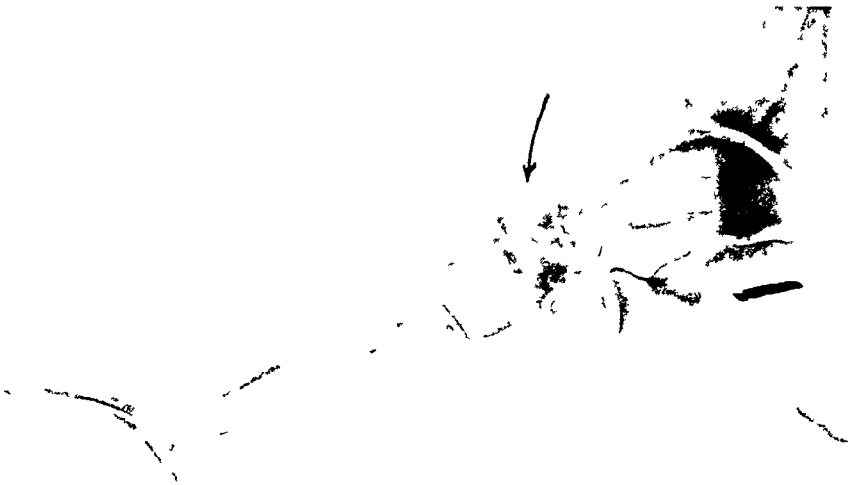


Fig 3—Roentgenogram of the right foot, taken five months before death. The dense periphery and fragmentation of the scaphoid bone may be noted. The patient had exquisite tenderness over this bone.

*Autopsy*—A large osteogenic sarcoma of the right scapula was found, invading the whole anterior and upper part of the bone, with infiltration into the supraspinous and infraspinous muscles. Visceral metastases were not found. A profound anemia was present. The yellow marrow of the femurs was entirely replaced by dark red, apparently regenerating marrow.

*Histologic Examination*—An osteogenic sarcoma was seen, in which there was considerable cartilage. In places, the growth was cellular, with mitotic figures and hyperchromatism, in other places, it was sclerotic. New formation of bone was common.



Fig 4—High power magnification of the osteogenic sarcoma tissue. Tumor mitoses and hyperchromatism may be noted.

The bone marrow showed a regenerative leukopenic anemia of the megaloblastic type, similar to that described as having occurred in three other fatal cases<sup>1</sup>.

Sections from the scaphoid bone of the right foot showed a radiation osteitis, the marrow being replaced by loose, gelatinous, myxomatous, fibroblastic tissue, in which there was considerable fat.

*Demonstration of Radioactivity in the Bones by Photographic Methods*—Dental films in their original packets, when strapped to the bones, showed photographic impressions in from fourteen to thirty days. The outlines of metal clips, coins and the like placed between the bone and the surface of the film were clearly

visible. These shadowgrams were produced by beta and gamma rays coming from deposits in the bones, the alpha rays being screened and filtered out by the paper of the dental pack.

The bones, when placed directly on photographic plates or films, produced photographic impressions in as short a period as three days. After seven days' exposure, the irregular distribution of the radioactive deposits could be plainly ascertained with typical alpha penciling.

Bones incinerated to a white ash and given thirty days in which to regain their equilibrium, when placed on photographic films, produced photographic impressions in from two to three days' exposure. The sarcoma when ashed and treated similarly showed only faint radioactivity. This was undoubtedly due to the impossibility of separating portions of the scapula from the new bone formed in the osteogenic sarcoma.



Fig 5—Photographic impressions of the head of the humerus and the shaft made by laying dried bones directly on the film. The duration of the exposure was five days. The exposure is due to alpha, beta and gamma rays, since there was not any screening. The irregular concentration in the bones may be noted, especially the large amounts in the cortex of the shaft, also the typical alpha penciling. In this figure, there is a reversal of the black and white of the original negatives.

*Demonstration of Radioactivity in the Bones by Scintillation Methods*—When portions of dried bone from various parts of the skeleton were held near a screen of phosphorescent zinc sulphide uncontaminated by radioactive substances and the screen was examined under a large magnifying glass, the latter showed typical scintillations. This was absolute proof of radioactivity, for each scintillation represented the light produced by the collision of an alpha particle (a double-charged nucleus of helium) against aggregates of zinc sulphide molecules. The bombardment of the alpha particle could undoubtedly have been heard if proper radio amplifiers had been used.

*Demonstration of Radioactivity in the Bones by Means of an Alpha Electro-scope*—Samples of bones, after being dried in an electric oven, showed positive

evidence of radioactivity when placed in the lower chamber of an alpha electro-scope of the Lind type

After the bones had been incinerated to white ash and had been given thirty days in which to regain their equilibrium, the increased leak due to radioactivity was easily demonstrable with the alpha electroscope

*Chemical Extraction with Determination of the Amount of Radioactivity*—After samples of bone had been incinerated in the electric oven to a white ash with an excess of carbon, a paste of the ash was made with barium chloride and hydrochloric acid. This was boiled with hydrochloric acid and distilled water and filtered while hot. The precipitate was dried, incinerated and after thirty days measured for radiothorium. Sulphuric acid was added to the filtrate, and, after being left to stand for precipitate, the mixture was boiled and then filtered while hot so that the calcium sulphate might be held in solution. The precipitate was again dried, incinerated and after thirty days measured for radium and mesothorium. By this method, a calculation was made, after a reading with the gamma electrometer against known standards, which showed that the entire skeleton in this case contained about 50 micrograms of radioactive substances, in which mesothorium predominated.

Concerning the amount of radioactive substance recoverable at autopsy in these cases, it is of interest to consider my previous experience. The amounts recovered were small. In the first case seen by one of us (M), that of a chemist who died from a rapidly progressing anemia of the regenerative type, the amount of radioactive substances present in the entire skeleton was estimated by the company's physicist to be about 14 micrograms, of which 45 per cent was radium and the remainder mesothorium. At that time we were not aware of the importance of the cases, and because of the restrictions placed on the performance of the autopsy, we were able to submit only a few of the lumbar vertebrae to the physicist for examination. In the next case, we had a better opportunity. By chemical methods, the radioactive substances were extracted, and it was estimated that the skeleton contained about 180 micrograms, of which 70 per cent was mesothorium and the products of its decay. In the third case, 150 micrograms of radioactive substances was found. In a case described by Flinn,<sup>2</sup> in which the gamma electroscope was used during life, he estimated that about 100 micrograms was present in the body. In another case examined by St. George and Gettler, 48,282 micrograms was recovered from the bones, liver and lungs. It may be seen, therefore, that the lethal amount, if there is such a quantity in these cases is extremely small. Judged by former experience, the amounts deposited in the body as insoluble sulphates sufficient to cause death by production of anemia of the regenerative or aregenerative type, or of necrosis of the jaw from an infection superimposed on a radiation osteitis, ranged from 14 to 180 micrograms. Our contention has always been that if there is enough radioactive substance deposited in the bones to secure photographic impressions in from five days' to two weeks' time, then during life there must have been sufficient radiation from these deposits to cause, in time, exhaustion of the blood-forming centers.

#### COMMENT

Several features in this case, combined with facts ascertained in a previous study of cases of occupational radium-mesothorium poisoning, have led us to believe that the preexisting deposits of radioactive sub-

<sup>2</sup> Flinn, F. B. A Case of Antral Sinusitis Complicated by Radium Poisoning, *Laryngoscope* **37** 341 (May) 1927

stances in the bones in this case played an important etiologic rôle in the subsequent development of the sarcoma. Of course, this is an alluring theory, which at present is not provable. The arguments for and against it may be summed up, as follows:

1 There was clinical evidence during life, supported by roentgenograms, that peculiar changes existed in the bones long before the appearance of the sarcoma. These were noted chiefly in the head of the right humerus, the acromium and the body of the right scapula and in the scaphoid bone of the right foot. They were of the nature of a radiation osteitis.

2 Microscopic sections of the scaphoid bone, removed at autopsy, showed a lesion that was indistinguishable from the irradiation osteitis produced by heavy external irradiation, as described by Ewing.<sup>3</sup>

3 Anything approaching a sarcomatous transformation in irradiation osteitis due to heavy external irradiation, as seen by radiotheraputists, has never been recorded. In fact, the general observation is that the process is more apt to become sclerotic, inactive and acellular.

The effects of single or repeated doses of external irradiation, however, must be quite different from those due to a never ceasing radiation coming from fixed deposits of radium and mesothorium in the bones. Furthermore, in all previously reported injuries of body or tissues as due to radiation and irradiation, the alpha rays never played the important rôle that they did in these cases. Here 95 per cent of the radiation was alpha, which biologically and chemophysically is much more destructive to body tissues than either beta or gamma radiation. In no previous experience have the internal vital organs been constantly exposed to their deadly effect for periods of years, for, in the case of all forms of external therapeutic irradiation, the alpha particle is usually screened or cannot penetrate more than 1 mm. of skin.

4 There was clinical evidence during life, supported by roentgenograms, that the sarcoma started in an area that previously was the seat of a radiation osteitis, while surrounding areas, also the seat of an osteitis, were not affected.

5 It should also be noted that while internal metastases and metastases to the bones were not observed in this case, there was a profound anemia, which at autopsy was shown to be a regenerative, leukopenic anemia, the femurs being filled with dark red marrow. This same type of anemia was found in three other fatal cases among watch dial painters, and was described as due to the effects of constant bombardment of the adjacent blood-forming centers especially by alpha particles.<sup>1</sup> Of course the same type of marrow has been seen in other

3 Ewing, James. Radiation Osteitis, *Acta radiol.* 6: 399, 1926.

diseases, notably addisonian anemia, and by Ewing<sup>4</sup> in large areas of bone the seat of spontaneous osteogenic sarcoma having nothing to do with radium

6 The part played by trauma in this case is difficult to determine. Many surgeons would find an adequate cause for the sarcoma in the fall followed by limited motion and pain in the shoulder and the insult of an exploratory operation that did not disclose any pathologic change. We have always been of the opinion that single falls and external violence in the production of osteogenic sarcoma have been greatly exaggerated. They do not offer a satisfactory explanation. Trauma, however, cannot be entirely ignored. In this connection, the remarks of Ewing<sup>5</sup> are of interest. "The idea that trauma, or any other factor, may lead to the development of sarcoma at the ends of long bones which are previously normal, is, I think, without satisfactory foundation. I have examined many cases of supposed traumatic origin and nearly always found that the tumor preceded the trauma. The high proportion of traumatic bone sarcomas reported by some observers seems to be obtained by very uncritical study. The previous integrity of the part can rarely be determined with reasonable certainty, and cannot be assumed on the statement of the biased patient." Kessler,<sup>6</sup> medical director of the New Jersey Workmen's Compensation Bureau, informed us that in 56,000 injuries examined by him, the result of industrial accidents, he observed only nineteen alleged malignant conditions attributed to trauma. Of the nineteen cases, but six were fairly well proved (the compensation law giving the employee the benefit of the doubt). Sarcoma of the bone was found in only one instance.

7 Since the cause of osteogenic sarcoma is unknown, the great majority of cases must be classed as spontaneous in origin. Why is not this case, therefore, of the same origin? Against this assumption is the incidence. Ophuls,<sup>7</sup> in an analysis of 3,000 autopsies, encountered sarcoma of the bone in only two cases, or 0.06 per cent. During the years from 1918 to 1927 inclusive, of 134,500 admissions to the Newark City Hospital (850 beds), only 14 (0.0001 per cent) were for osteogenic sarcoma of a long bone. Primary bone tumors, then, are of unusual occurrence. The incidence of two osteogenic sarcomas in fifteen persons dying as the result of an occupational poisoning by radioactive substances is too high to be mere coincidence.

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4 Ewing, James    Personal communication to the author

5 Ewing, James    *Neoplastic Diseases*, ed 3, Philadelphia, W. B. Saunders Company, 1928, p. 310

6 Kessler, H. H.    Personal communication to the author

7 Ophuls, William    *A Statistical Survey of Three Thousand Autopsies*, Stanford University Press, Stanford University, 1926

8 It is of great importance to radiotherapeutists that they should recognize the possibility of the production of a malignant growth by undue or excessive irradiation. The radiation in these dial painters was unique, in that it was constant over every second of the day for years. In addition, the alpha particle played an important part, never played by it before, according to previous records of the deleterious effects of irradiation. What evidence is there that single or repeated interrupted exposures to x-rays or radium produce malignant changes in the tissues? With the exclusion of many reports of epitheliomas that have been engrafted on irradiation dermatitis, which are now becoming rare owing to better protective technic, there still remains evidence in the literature that malignant changes, especially sarcomatous changes, have followed irradiation. Only a few of these instances need be mentioned. A sarcoma following roentgen treatment for joint tuberculosis was reported by Baumann.<sup>8</sup> A sarcoma of the uterus and ovaries following irradiation was reported by Vogt.<sup>9</sup> A sarcoma of a cicatrix after an irradiation dermatitis was reported by Complani,<sup>10</sup> and instances of roentgen sarcoma were recorded by Pforringer.<sup>11</sup>

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8 Baumann, M. Roentgen Sarcoma After Irradiation for Joint Tuberculosis, *Strahlentherapie* **26** 610, 1927.

9 Vogt, E. Sarcoma of Uterus and Ovaries Following Irradiation, *Fortschr a d Geb d Rontgenstrahlen* **35** 44, 1926.

10 Complani, M. Sarcoma of Cicatrix Following Radiation Dermatitis, *Radiol Med* **14** 841 (Oct) 1927.

11 Pforringer, S. Roentgen Ray Sarcoma, *Strahlentherapie* **26** 610, 1927.

# VARIATIONS AND ANOMALIES OF THE VENOUS VALVES OF THE RIGHT ATRIUM OF THE HUMAN HEART \*

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The eustachian valve or valve of the inferior vena cava and the thebesian valve or valve of the coronary sinus are normally both remnants of the right valve of the sinus venosus

## EMBRYOLOGY

In the embryonic development of the heart, according to the works of His,<sup>1</sup> Born<sup>2</sup> and Rose,<sup>3</sup> the single atrial cavity is divided into its two definitive chambers in the following manner. The septum primum arises from the mid-dorsal wall of the atrium and eventually fuses with the endocardial cushions at the juncture of the atrial and ventricular cavities. A perforation of the septum primum occurs to form the foramen ovale. This is subsequently closed by the fusion of the left valve of the sinus venosus and the septum secundum, which appears in close proximity to the septum primum as an outgrowth from the ventral and the caudal wall of the right atrium (fig 1)

The right horn of the sinus venosus lags somewhat in its evolution and is taken up in the wall of the right atrium, which causes the opening into the right atrium of the superior and the inferior venae cavae. The right valve of the sinus venosus at one time nearly divides the right atrium into two chambers, but later it becomes progressively lower, its cephalic portion remaining as the crista terminalis, its caudal portion being divided to form the valve of the inferior vena cava (eustachian valve) and the valve of the coronary sinus (thebesian valve). As the left horn of the sinus venosus is migrating across the posterior wall of the atrium during the stage of absorption of the remainder of the sinus, it projects into the lumen of the atrium as the inferior sinus septum and divides the caudal portion of the right sinus valve into these two definitive valves. The opening of the left horn of the sinus venosus is

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\* Submitted for publication, Oct 8, 1928

1 His, W. Anatomie menschlicher Embryonen, Leipzig, F C W Vogel, 1885

2 Born, G. Ueber der Bildung der Klappen, Ostien und Schweißedewande im Saugetierherzen, Anat Anz **3** 606, 1888, Beiträge zur Entwicklungsgeschichte des Saugethierherzens, Arch f mikr Anat **33** 284, 1889

3 Rose, C. Beiträge zur vergleichenden Anatomie des Herzens der Wirbelthiere, Morphol Jahrb **16** 27, 1890



the left duct of Cuvier, which is thus pulled over to a place beneath the orifice of the inferior vena cava and persists in part as the coronary sinus. The septum spurium is a vertical ridge formed by fusion of the right and the left valves of the sinus venosus on the dorsal and the cephalic walls of the right atrium, and this is also taken up into the wall of the atrium as it expands. It partly remains, however, to form the uppermost portion of the crista terminalis, where it separates sharply the orifice of the superior vena cava from the atrial appendage.

The eustachian valve serves to direct the blood in embryonic life from the inferior vena cava into the left atrium through the foramen ovale. The thebesian valve possibly serves to prevent regurgitation of the blood into the coronary sinus during auricular systole. This supposition, however, seems unlikely since the thebesian valve is usually incompetent, that is, it is not sufficiently extensive to close the orifice of the coronary sinus, or, if so, is usually fenestrated.

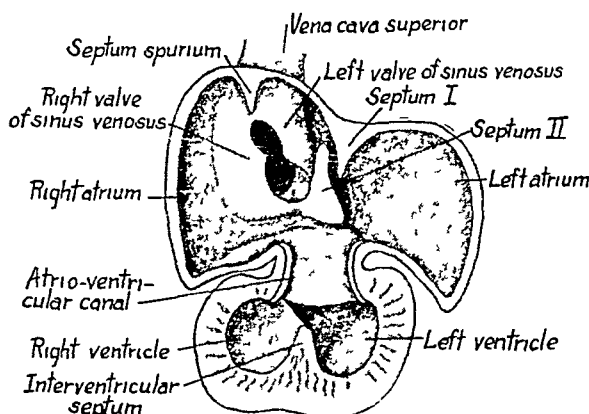


Fig 1—Inner view of the dorsal wall of the heart of a 10 mm human embryo. Drawn from a Ziegler model of one of His' embryos (after Jordan, H. E., and Kindred, J. E. *Textbook of Embryology*, New York, D. Appleton & Company, 1926).

#### DESCRIPTION OF THE ADULT VALVES

The eustachian valve is usually a muscular and membranous fold in the right atrium extending posteriorly from below the fossa ovalis and then upward just anterior to the orifice of the inferior vena cava, in the upper portion of which it is lost. Its free margin is concave and directed upward and forward, its adherent border is convex and directed downward and backward. One of its surfaces is turned laterally toward the atrium, the other medially toward the vessel. The lower portion is a transverse muscular ridge (the sinus septum) continuous with the limbus fossae ovalis, the upper portion is usually membranous. Often the membranous part of the valve contains thin strands of ordinary cardiac muscle, especially in its attached portion. Often, also, it has fenestrae, and sometimes has thin strands of endocardium attached at two points.

along its edge or forming a little network there. The valve is usually not more than 1 cm wide in the adult. In some cases, the eustachian valve is inconspicuous or entirely lacking. In others, it is broad, projecting far into the right atrium. Sometimes it is thin and flabby, sometimes fibrous and taut.

The thebesian valve is directly below the lower portion of the eustachian valve in the space between this and the edge of the atrioventricular foramen at the juncture of the lower portion of the interatrial septum and the posterior wall of the atrium in close association with the mouth of the coronary sinus, to which it is usually placed laterally. It is frequently semilunar or crescentic with its anterior free edge concave, and its posterior attached edge convex. It is often fenestrated or made up of a network of threads. In fact, its size and form are extremely variable. It may be absent, represented merely by a thin, narrow ridge

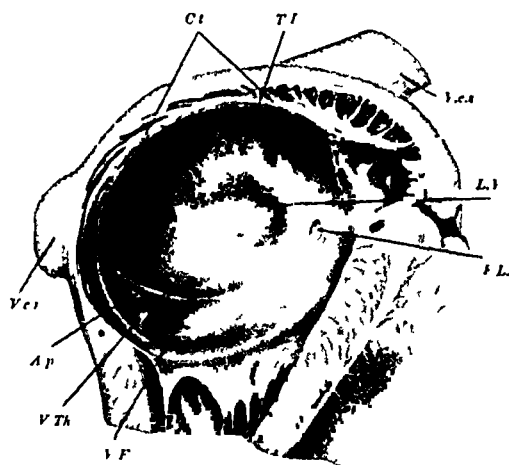


Fig 2—Right atrium with the lateral wall removed to show the relationship of the orifices of the atrium and the usual forms of the eustachian and the thebesian valves, *VE*, eustachian valve, *VTh*, thebesian valve, *Ap*, auricula posterior, *Vci*, inferior vena cava, *Ct*, crista terminalis, *TL*, tuberculum loweri, *Vcs*, superior vena cava, *L.V.*, limbus vieussensii, *FL*, Foramen Lannelongeus (after Tandler, Julius, in Bardeleben Handbuch der Anatomie des Herzens, Jena, Gustav Fischer, 1913)

on the posterior edge of the mouth of the coronary sinus, or present as a large membrane completely covering the sinus orifice. It may even be anterior to the orifice, placed obliquely, transversely or vertically across it. Usually, it is thin and translucent. Sometimes there is a definite connection between it and the eustachian valve. The orifice of the coronary sinus with its valve often lies in a saccular depression between the lower portion of the eustachian valve and the atrioventricular rim, this is the appendix auricularis posterior of His or the subeustachian sinus of Keith. Figure 2 shows the most common form of the valves and their relationships in the atrial cavity.

## ANOMALIES OF THE VALVES OF THE RIGHT ATRIUM

Anomalies of these valves are dependent on the degree of the regression of the right and the left valves of the sinus venosus, the septum spurium and the sinus septum. Hearts with defective development of the interatrial septum may contain all grades of persistence of these four structures, but the completely developed heart presents relatively few types of anomalies of the valves. In the adult heart, rudiments of the right venous valve are found at the sharp anterior rim of the orifice of the inferior vena cava, extending upward to the upper portion of the crista terminalis and downward across the orifice of the coronary sinus toward the tricuspid orifice. Remnants of the left venous valve are situated on the interatrial septum in the posterior region of the annulus fossae ovalis and the intervenous tubercle (*tuberculum loweri*), which is merely an eminence superior to the fossa ovalis between the orifices of the venae cavae. Residual structures of the septum spurium are found anterior to the mouth of the superior vena cava near the interatrial septum. Remnants of the sinus septum are seen normally in the muscular ridge that extends from the lower end of the limbus fossae ovalis to the inferior part of the rim of the orifice of the inferior vena cava and becomes a part of the normal eustachian valve. If the inferior sinus septum has merely fused with the right venous valve and has not divided it, the eustachian and the thebesian valves are formed as a continuous fold with an attachment to the wall of the atrium in the region of the inferior sinus septum. If the inferior sinus septum has failed entirely, the two valves are seen as a simple membrane or reticulum unattached except perhaps posteriorly to the wall of the atrium.

## REVIEW OF THE LITERATURE

So far as I know, a review of the literature regarding these anomalies has never been made.

Lindes<sup>4</sup> described the heart of an infant, in which there was a single atrial cavity and other congenital anomalies. The structures present were similar to those that Ruge,<sup>5</sup> in case 2, interpreted as persistent right and left venous valves.

Maier<sup>6</sup> reported an adult heart in which there were two folds in the right atrium, interpreted by Ruge, in case 13, as a persistent right venous valve and a remnant of the septum primum.

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4 Lindes, G. Ein Beitrag zur Entwicklungsgeschichte des Herzens. Inaug. Dis., Dorpat, 1865.

5 Ruge, Hans. Ueber Defecte des Vorhofsscheidewand des Herzens, Virchows Arch. f. path. Anat. **126** 323 1891.

6 Maier, R. Zur Casuistik der Herzfehler, Ber. u. d. Verhandl. d. nat. Gesellsch. **4** 478, 1867.

Schmidt<sup>7</sup> stated that in adults now and then the eustachian valve is lengthened upward to the anterior edge of the superior vena cava, and that sometimes a broad communication exists between the eustachian and the thebesian valves. These forms represent a slight incompleteness of regression of the right venous valve to its final adult vestige as the eustachian and the thebesian valves. These forms are, indeed, not uncommon.

Rokitansky<sup>8</sup> presented two cases of anomalous membranes in the right atrium that Chiari<sup>9</sup> later concluded represented the right venous valve (Rokitansky's case 16) and the left venous valve (Rokitansky's case 17).

Lauenstein<sup>10</sup> described a variation of the valves that he had observed five times in 100 necropsies. In these hearts, the two valves, eustachian and thebesian, which are ordinarily separate, were formed by one extensive membrane. This common valve was a simple membrane in one case, a fenestrated membrane in three cases and a network of exceedingly fine fibers in another case. In one case, it was so large that it divided the atrium into an anterior and a posterior chamber.

Moore<sup>11</sup> reported a case in which there was a large muscular fold beginning just below the fossa ovalis and stretching from the interatrial septum near the orifice of the inferior vena cava to the posterior wall of the right atrium. He described a similar case in another report and stated that he had met with one other example. These were probably much exaggerated eustachian valves with an excessive development of the inferior sinus septum.

Leo<sup>12</sup> described the heart of an infant, in which there were multiple anomalies and an abnormal membrane in the right atrium bounding the orifice of the superior vena cava and a common eustachian and thebesian valve. The interpretation in this case could not be established.

Preisz<sup>13</sup> reported a case (case 5) of multiple anomalies, among which was a great sieve-like flap at the right border of the inferior vena cava.

7 Schmidt. Bidrag til kundskaben om huerkets udviklingshistorier, Nord med Ark **2** 1, 1870.

8 Von Rokitansky. Die Defecte der Scheidewande des Herzens, Vienna, 1875.

9 Chiari, H. Ueber Netzbildungen im rechten Vorhofe des Herzens, Beitr z path Anat u z allg Path **22** 1, 1897.

10 Lauenstein, Carl. Varietät der Klappen des rechten Atrium, Virchows Arch f path Anat **68** 632, 1876.

11 Moore, Norman. Variety in the Structure of the Heart, Tr Path Soc, London **34** 31, 1883.

12 Leo Hans. Ueber einen Fall von Entwicklungshemmung des Herzens, Virchows Arch f path Anat **103** 503, 1886.

13 Preisz, Hugo. Beiträge zur Lehre von den angeborenen Herzanomalien, Beitr z path Anat u z allg Path **7** 245, 1890.

and the coronary sinus, which, according to Ruge, in case 17, corresponded to the right venous valve

Stadler<sup>14</sup> reported a case of multiple anomalies of the heart in which there was a fold arising from the inferior vena cava and another passing from the inferior vena cava on the right to the inferior and posterior end of the incompletely developed interatrial septum. Ruge, in case 9, and Chiari both interpreted the first fold as a remnant of the right venous valve and the second as the persistent horizontal ridge developing in embryonic life between the inferior vena cava and the coronary sinus (sinus septum)

Przewoski<sup>15</sup> wrote concerning anomalous chordae tendineae in the heart of man and described networks of fibers near the mouths of the great veins in the right atrium and along the limbus fossae ovalis. He believed these to be remnants of the venous valves of the embryo. His interpretation antedated Chiari's more detailed and precise description and explanations.

The most interesting anomaly of the eustachian valve is that described by Chiari<sup>9</sup> and known since as "Chiari's network." This consists of a network of fine or coarse fibers in the right atrium, its attachments extending from the interatrial septum or the upper portion of the crista terminalis to the thebesian and the eustachian valves or to the region of the orifices of the coronary sinus and the inferior vena cava. Chiari reported eleven cases, in one of which the network was responsible for the death of the patient, a young man aged 24. In this case, there was extensive pulmonary embolism, the source of which was apparently a small thrombus lodged in the confluence of the fibers of the network. Chiari concluded that the malformation represented the remains of the septum spurium and the right venous valve. None of Chiari's cases showed any other relevant congenital anomalies except an additional case of a related anomaly. The heart in this case retained large remnants of both the right and the left venous valves. Chiari called attention to the fact (as shown by Born in mammals and by Rose in monotremes and marsupials) that in these animals the venous valves persist partly or entirely. He stated that Born had also noted that in new-born human beings a semilunar ridge is often to be found under the anterior rim of the opening of the superior vena cava at the juncture of the anterior and the medial walls of the right atrium, which according to its position and

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14 Stadler, O. Ueber eine seltene Missbildung des Herzens, Verhandl. d. phys.-med. Gesellsch. **24** 61, 1890-1891.

15 Przewoski, E. Anomaliae chordae cordis humani, valvulae venae cavae superioris, Pam. Towarz. Lek. Warszaw. **92** 400, 1896, Cystenformige Veränderung der Semilunarklappe der Aorta. Phlebolith des rechten Vorhofes, Sinus venosus fossae ovalis (abstr.), Centralbl. f. allg. Path. u. path. Anat. **8** 152, 1897.

direction is considered a remnant of the free edge of the septum spurium, a trace of which is sometimes recognized even in adults

A Weber<sup>16</sup> described a remarkable example of Chiari's network. Besides the main network there was a network of filaments along the posterior edge of the membranous portion, some of the filaments hanging free and supporting a small secondary membrane. Weber interpreted the main network as being derived above from the right venous valve and below from the inferior sinus septum, the upper portion corresponding to the eustachian valve, the lower to the thebesian. He believed that in Chiari's cases, also, the lower attachments of the network were remains of the inferior sinus septum and not displacements of the right venous valve. He referred to the work of Milne-Edwards, which showed that, in certain adult birds, the sinus portion of the right atrium is separated by fleshy strands from the atrial portion proper. The smaller network, he believed, represented remains of the left venous valve.

Swan<sup>17</sup> reported, as an example of Chiari's network, a valvelike flap of endocardium lying against the fossa ovalis on the right side and attached to the annulus fossae ovalis by anastomosing bands closely resembling chordae tendineae. This is certainly not Chiari's network but probably a remnant of the left venous valve which did not completely fuse with the septum secundum. Minor degrees of this anomaly are not infrequent, as noted by Lower, A. Weber, Oppenheimer, Mollendorf and others.

Le Count<sup>18</sup> recorded an instance of Chiari's anomaly, in which the network was entirely below the orifice of the inferior vena cava.

Looser<sup>19</sup> presented an example of Chiari's network, in which there was a thrombus about 2 cm. in diameter attached to a few fibers of the net. A hemorrhagic embolic infarct was present in the left lung, and also thrombi in both femoral veins, so that it was impossible to determine whether the thrombus on the network developed primarily at that site or had been carried there from the venous thrombi and had grown to its final size. Looser considered that these networks may be remnants of the right venous valve, the left venous valve, the septum spurium or the sinus septum. He stated that rudiments of the right venous valve should be looked for at the thebesian valve, the upper part of the eustachian valve and the crista terminalis, remnants of the left venous valve should

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16 Weber, A. Formation reticulée de l'oreillette droite et fosse ovale anormale d'un cœur humain adulte, *Bibliog. anat.* **6** 17, 1898.

17 Swan, J. M. Fenestration of the Right Auricle, *Proc. Path. Soc.* **2** 71, 1898-1899.

18 Le Count, E. R. Network Formations in the Right Auricle, with Demonstration of a Specimen, *Tr. Chicago Path. Soc.* **5** 309, 1901-1903.

19 Looser. Ueber die Netzbildungen im rechten Vorhofe des Herzens, *Inaug. Dis.*, Zurich, 1902.

be looked for at the interatrial septum in the arched line which connects the left borders of the two venae cavae, and vestiges of the septum primum anterior and medial to the mouth of the superior vena cava near the interatrial septum. Fairly large remnants of the right venous valve are by far the most common, those of the left venous valve are more rare, and any notable remnant of the sinus septum is unusual. Looser disagreed with Chiari, maintaining that the latter's eleven networks were all remnants of the right venous valve without any involvement of the septum primum. He recognized the anomaly in which the eustachian and the thebesian valves are replaced by a common reticulum owing to a lack of fusion of the right venous valve with the sinus septum which normally becomes the lower part of the eustachian valve and separates this from the thebesian valve. Remnants of the right venous valve are sometimes found at a greater or less distance from their normal site, probably because of irregularities in the growth of the endocardium. A relatively common displacement is that of the threads from the crista terminalis toward Lower's tubercle. The cause of this displacement is probably the proximity of the mouths of the large veins and a distortion of the endothelium during the rapid growth of the heart. There are many transitions from the normal condition of the eustachian valve and the thebesian valve to these reticulate structures.

Ebbinghaus<sup>20</sup> reported a case of Chiari's network and accepted Chiari's explanation.

A. Weber<sup>21</sup> discussed the question of remnants of the left venous valve as commonly seen. At the postero-inferior part of the fossa ovalis are frequently found punched-out areas beneath which a little probe can be moved a variable distance over the subjacent endocardial surface. This space passes anteriorly into the fossa ovalis and posteriorly toward the inferior vena cava. It is the part of the fossa ovalis that lacks the projecting limbus. Weber interpreted this perforated portion as a remnant of the left venous valve, the space beneath representing the inter-septovalvular space of Rose. The left venous valve fuses not only with the septum secundum to form the limbus of the ostium secundum but also directly with the septum primum anterior to the posterior rim of the septum secundum. Weber quoted Giossei as having found a persistence of the left venous valve in a certain number of *Cheiroptera*, and Devez in the American *Didelphys*. The echidna (monotreme) has a valve for each vena cava and a valve common to both. The ornithomynchos has a common internal valve represented by a simple musculomembranous

20 Ebbinghaus, H. Zur Kasuistik der kongenitalen Herzfehler und deren möglichen Folgen, München med Wchnschr 51 797, 1904.

21 Weber, A. Restes de la valvule veineuse gauche dans le coeur humain adulte, Bibliog anat 13 11, 1904.

ridge Other animals having an internal valve in the inferior vena cava are *Myrmecopha tetradactyla*, the jaguar and the babai

Wortmann<sup>22</sup> described an infant's heart presenting many unusual anomalies In place of the eustachian valve, there was a bulging, sac-like membrane, at one edge of which was attached a spherical, blackish thrombus, "the size of a small pea" There was also an independent network along the left edge of the orifice of the inferior vena cava with threads attached to Lower's tubercle The saclike membrane was a residuum of the right venous valve, the network a remnant of the left venous valve

In Thilo's Inaugural Dissertation,<sup>23</sup> in 1909, were descriptions of five cases of reticula in the right atrium, two of which were similar to Chiari's first four cases In one of these, a grayish-red, "pea-sized," spherical thrombus was attached to the network There was an embolic infarct of the lung, and also a thrombus in the common iliac vein, so that the source of the pulmonary thrombus may have been from this and not from the thrombus of the reticulum

Lesieur, Froment and Cremieu<sup>24</sup> reported an instance of an "anomalous thebesian valve associated with a large patent foramen ovale" They believed the flap to be a remnant of the left venous valve which had failed to fuse with the septum secundum to close the foramen ovale

Mollendorff,<sup>25</sup> described a heart containing remnants of both the right and the left venous valves The sinus septum had not divided the right venous valve into its two definitive valves

Haas<sup>26</sup> reported an unusual case There were three groups of threads forming a network and replacing the eustachian and the thebesian valves The uppermost group was attached to the region of the crista terminalis beside the right edge of the superior vena cava On the network hung an embolus 6 cm long and surrounded twice in its middle by a thread This embolus had undoubtedly come from a thrombus in the left femoral vein and had become ensnared in the network, thus preventing fatal pulmonary embolism

22 Wortmann, W Ueber eine seltene Herzmissbildung Zugleich ein Beitrag zur Frage der Netzbildungen im rechten Vorhofe, Inaug Dis, Wurzburg, 1909

23 Thilo, L Zur Kenntnis der Missbildungen des Herzens, Inaug Dis, Leipzig, 1909

24 Lesieur, C, Froment, J, and Cremieu, R Coexistence d'une communication interauriculaire et d'une anomalie de la valvule de thebesius, Lyon med **116** 1045, 1911

25 Von Mollendorff, Wilhelm Ueber abnorme Erhaltung der Sinusklappen im rechten Vorhof eines menschlichen Herzens, Anat Anz **40** 406, 1912

26 Haas, W Ueber einen weiteren Fall von Netzbildungen im rechten Vorhof mit einem in denselben verfangenen Embolus, Inaug Dis, Karlsruhe, 1916



F P Weber<sup>27</sup> redescribed Ebbinghaus' case, in which he had seen the heart, and reported two of his own. He considered these to be examples of Chiari's network, but they were probably merely exaggerated "openwork" eustachian valves.

Jordan's two cases<sup>28</sup> were good examples of Chiari's network. He mentioned a third case seen two years before. Jordan's conclusion was "As these bands arise from the interatrial septum in the region developed from the left valve of the sinus venosus and also from the crista terminalis which is the remains of the cephalic portion of the right valve of that sinus and as they insert in close proximity to and directly on the thebesian and eustachian valves it seems that Chiari's explanation is proper. However, the left valve of the sinus venosus is also involved." Jordan noted that both the patients had auricular fibrillation at the time of death, and he speculated as to the rôle the network might play in producing this arrhythmia because of a "close relationship between the network and the conducting system."

Wurm<sup>29</sup> reported a case of corrected transposition of the great vessels and described a network in the left side of the right atrium which he called an instance of Chiari's network. This type of reticulum is not similar to Chiari's cases, however, and such threads are not extremely rare.

#### METHOD OF OPENING THE HEART

I have studied the eustachian and the thebesian valves in 120 hearts collected as a routine. In order to preserve the eustachian valve intact it was necessary to modify the technic of opening the heart.

In a heart opened in the usual routine manner, the eustachian valve is cut almost directly through its middle by the scissors, as they pass between the orifices of the two venae cavae. If the valve is flimsy, as it often is, its two halves collapse against the wall of the atrium and are not seen unless special notice is taken of them. When it is desired to examine the valves, one may first look through the open end of the inferior vena cava into the right atrium, and, should an anomalous valve be observed, one may then open the right atrium by an incision anterior and parallel to the anterior rim of the inferior vena cava and then across to the tip of the atrial appendage from the lower end of this opening. This method gives ample exposure of the interior of the right atrium and also preserves the sino-auricular node should the examiner desire to study this microscopically. In removing the heart from the body, care must be taken, in cutting the inferior vena cava, not to encroach on the right atrium.

27 Weber, F P. Interesting Cases in Which a So-Called Chiari's Net Was Found in the Right Auricle of the Heart, with or without the Presence of any other Congenital Cardiac Abnormality, *Internat Clin* 3 43, 1920.

28 Jordan, W R. Two Cases of Chiari's Network, *Arch Path* 2 840 (Dec) 1926.

29 Wurm, H. Angeborener Herzfehler mit "korrigierter" Transposition der grossen Gefässe, *Virchows Arch f path Anat* 263 123, 1927.

VARIATIONS OF THE ADULT VALVES<sup>30</sup>

The structure of the eustachian valve varies, but it takes relatively few forms. In the 120 hearts studied with special emphasis on these valves, the eustachian valves could all be classified as of one or the other of six anatomic types. In several hundred other hearts observed later, all of the valves conformed to one or the other of these types. A brief description of each type of valve with the relative number of hearts in which it was found, follows:

1 The valve absent (seventeen cases). The sinus septum and the anterior rim of the inferior vena cava were all that denoted the previous existence of a right venous valve, except for the thebesian valve, which was present in sixteen cases and absent in one case.

2 A simple nonfenestrated flap or membrane (sixty-nine cases). The usual form was crescentic. It varied from a narrow little fold along the anterior edge of the orifice of the inferior vena cava, to a broad membrane 2.3 cm wide. The valve, in some cases, was a thin, flabby, transparent membrane distinct from the rim of the vena cava, and in some cases it was a tough, taut fold merging with the rim of the vena cava and the wall of the atrium. It sometimes had muscle fibers in it, especially thin, narrow strands near the attached edge.

3 A fenestrated semilunar membrane containing from one to many fenestrae (twenty-two cases). In one of the cases, it had accessory threads on its surface. In most of the cases, the valve was thin. Sometimes it was narrow or broad and veil-like.

4 A valve formed in part or entirely of a network of threads (seven cases). In some of the cases this looked like a cobweb.

5 Both the eustachian and the thebesian valves formed of one membrane (two cases). In one case the transverse sinus septum was lacking.

6 Chiari's network (three cases). One other instance of Chiari's network was found in a preserved heart.

Of the 120 hearts, twelve had definite connecting tissue between the eustachian and the thebesian valves. The average width of the simpler forms was 0.35 cm and the average length at the free edge 3.42 cm. The minimal width was 0.15 cm and the maximal 2.3 cm. The minimal length at the free edge was 1.7 cm and the maximal 7.5 cm.

The thebesian valve varied anatomically more than the eustachian. The thebesian valves in these hearts may be classified as follows:

1 The valve absent (thirteen cases). The coronary sinus opened directly into the atrial cavity.

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30 All descriptions and measurements of the valves are given as for a heart held with the long axis vertical, the observer looking at the right side of the interatrial septum.

2 A simple nonfenestrated fold attached to the posterior edge of the orifice of the coronary sinus (sixty cases) This varied from a narrow little rim to a broad membrane extending over the sinus orifice The predominating shapes were crescentic, semilunar and triangular The valve was usually thin

3 A simple fenestrated membrane (seventeen cases) This type varied from a thin crescentic flap to a large fold covering the orifice

4 A rather simple fold with one or more accessory threads (seven cases)

5 A simple vertical bar (two cases)

6 A valve consisting of fine threads only (four cases) In two of the cases, the threads formed a network in the sinus orifice In one, a thread ran obliquely across the orifice

7 A U-shaped fold with the sinus orifice between the limbs (five cases)

8 A valve represented by complicated membranes passing vertically across the sinus orifice (four cases)

9 The thebesian and the eustachian valves formed by one fold (two cases) In one of these cases, the transverse sinus septum was lacking

10 Miscellaneous type (six cases) (a) an inverted U-shaped fold with the sinus orifice between the limbs, (b) a crescentic fold with strands anterior to the sinus orifice, (c) a crescentic fold with a branch, (d) a network over the sinus orifice, (e) a large, fenestrated veil in the sinus orifice with anchoring strands, and (f) a triangular fold with one fenestra, attached to the inferior rim of the sinus orifice

Only three or at most four of these valves may be considered at all competent, that is, sufficient to close the orifice against a backflow The average horizontal width of the simpler forms of these valves was 0.6 cm and the average vertical width 1.05 cm The minimal horizontal width was 0.05 cm and the maximal 2.2 cm The minimal vertical width was 0.6 cm and the maximal 2 cm

In another series of hearts from fifty adults, the thebesian valves were of somewhat similar types

1 The valve absent (five cases)

2 A simple nonfenestrated fold attached to the posterior edge of the orifice of the coronary sinus (twenty-six cases)

3 A simple fenestrated membrane (nine cases)

4 A crescentic fold with accessory threads anteriorly (two cases)

5 A simple vertical bar (two cases)

6 A simple horizontal bar (two cases)

7 Miscellaneous types (four cases) (a) fenestrated vertical membrane anterior to the sinus orifice with a strand across the sinus orifice

to the posterior rim of the orifice, (b) a network with an accessory thread anterior to the sinus orifice, (c) a large, horizontal, fenestrated membrane in the sinus orifice extending far out anteriorly, with anchoring strands to the sinus inferiorly, and joining the eustachian valve at its posterior end, and (d) a membrane stretching obliquely across the sinus orifice with a vertical branch anterior to the orifice

The average horizontal width of those valves that could be measured was 0.78 cm and the average vertical width 1.03 cm. The minimal horizontal width was 0.15 cm and the maximal 2.3 cm. The minimal vertical width was 0.6 cm and the maximal 2 cm.

The simplest forms of the eustachian valve are usually associated with the simplest forms of the thebesian valve. When one is fenestrated the other is usually fenestrated also.

From this series of hearts, with the addition of a few other specimens, one can select a number of cases which illustrate a gradual progression from unusually large but structurally normal valves to those valves which show features due to some embryologic deviation. The group of hearts to be described includes all the types of anomalies that have been described in connection with the venous valves of the right atrium in the adult structure.

#### REPORT OF CASES

CASE 1—The eustachian valve was a large, tough, fenestrated semilunar membrane, 3.5 cm long at its free edge and 1.5 cm broad at its greatest width (fig. 3). Muscle strands were not visible macroscopically. Seen through the orifice of the inferior vena cava from without, the valve seemed almost to cover the orifice of the vein. The thebesian valve was similar, but much thinner, and the fenestrae were proportionately larger. There was nothing especially remarkable about these valves. They merely represented the more exaggerated type of the usual form.

CASE 2—The eustachian valve was an openwork, fibrous, white structure (fig. 4), which, in its upper and posterior portion, consisted of interlacing fibrous threads and strands. The free margin of the valve was 2.5 cm long and the greatest width measured 1.5 cm. If, instead of the fibers, this valve had contained more membrane, it would have closely resembled the valve in case 1. The thebesian valve was a simple semilunar fold.

CASE 3—The eustachian valve was a large, flabby, thin, white and much fenestrated veil-like membrane. The free edge measured 5 cm and the greatest width 2.3 cm. The thebesian valve was a large, nonfenestrated fold immediately below and almost continuous with the eustachian valve. It completely covered the orifice of the coronary sinus. The two valves together constituted a large remnant of the right venous valve of the embryo, but conformed to the type of valves found in adults.

CASE 4—A woman aged 65, died of congestive heart failure due to hypertension. The electrocardiogram revealed auricular flutter with an auriculoventricular block, shifting back and forth between 2:1 and 4:1 ratios, and an incomplete right bundle branch block with a QRS interval of 0.12 second. The heart weighed 684 Gm. The eustachian and the thebesian valves were formed by a continuous,

large, fenestrated membrane extending from below the orifice of the coronary sinus upward in front of the inferior vena cava to a broad attachment in the roof of the right atrium about 12 cm posterior to the median portion of the crista terminalis. This membrane was attached to the usual transverse muscular ridge that lies between the inferior vena cava and the coronary sinus (a remnant of the inferior sinus septum) and forms the lower end of the normal eustachian valve. The entire membrane measured 5 cm at its free edge and 16 cm at its widest part. It was of the type described by Lauenstein. In the nonfenestrated portion of the free edge was a flat band of cardiac muscle, 0.2 cm wide, which



Fig 3 (case 1)—The right atrium is opened to show a large, fenestrated, semilunar eustachian valve and a similar thebesian valve. *A* indicates the fossa ovalis, *B* the eustachian valve, *C* the thebesian valve and *D* the tricuspid valve.

was continuous with the musculature of the atrium above and with that of the transverse ridge below. Such a distribution of muscle raises the question whether the ring of muscle thus formed could have been the pathway of the simple circus movement of auricular flutter.

CASE 5—A man, aged 33, had been subject to chronic mitral endocarditis and auricular fibrillation. He died of congestive heart failure. The weight of the heart was 707 Gm. Both atria were greatly dilated, both ventricles greatly hypertrophied and the mitral orifice thickened, rigid and stenotic. The venous valves

were of the type described by Lauenstein, but the inferior sinus septum had failed to unite with the right venous valve. The two valves were a continuous thin membrane with a thin bridge between them (fig 5). This bridge formed an arch over the orifice of the coronary sinus, and the membrane was not attached to the wall of the atrium in the region of this arch. Both the upper and the lower portions of the common valve were expanded, somewhat triangular and fenestrated, and lay in different planes. Above, the valve was attached to the wall of the atrium just anterior to the lower half of the orifice of the inferior vena cava,



Fig 4 (case 2)—The right atrium is opened to show a large, openwork eustachian valve. *A* indicates the orifice of the inferior vena cava, *B* the eustachian valve, *C* the orifice of the coronary sinus and *D* the thebesian valve.

below, it fused with the endocardium by a wide base anterior to the orifice of the coronary sinus and a short distance above the tricuspid orifice.

CASE 6—In this case, also, the two valves were united in one large membrane. The transverse muscular ridge (sinus septum) was present but was connected with the common valvular fold by a little thread only. There was also a network on the posterior half of the fossa ovalis attached along the posterior rim of the limbus and by short bands to the endocardium covering the fossa ovalis (fig 6).

CASE 7—A man, aged 69, died from bronchopneumonia, following colostomy for carcinoma of the descending colon. In the left pulmonary artery was a fairly large antemortem thrombus. The heart did not show anything of note except the venous valves. There was a small, triangular membrane flanked by a thread on each side, which arose from the upper and anterior part of the rim of the orifice of the inferior vena cava (fig. 7). The small membrane and threads



Fig. 5 (case 5) —The lower interior of the right atrium is exposed to show a combination of the eustachian and the thebesian valve with absence of the inferior sinus septum.

quickly converged to be lost in the substance of a firm white thrombus, which was irregularly round with excrescences above and below. The thrombus measured 1.3 by 0.8 by 0.8 cm. From the lower end of the thrombus, some closely entwined threads emerged and passed downward and posteriorly. They were attached by a triangular membranous and filamentous base to the anterior rim of the inferior vena cava, the distance between the upper end of the upper attachment and the

lower end of the lower attachment on the rim of the vena cava being 27 cm. From the lower part of the entwined threads below the thrombus, a thread 28 cm long passed downward and was attached to the anterior edge of an extensive fenestrated thebesian valve, measuring 12 by 11 cm, which covered the orifice of the coronary sinus. Another shorter thread arose from the inferior sinus septum and passing downward was attached with this longer thread to the thebesian valve.



Fig 6 (case 6) —An exposure as in figure 5. The large common fold of the eustachian and the thebesian valves has been pulled to the side to show the network on the posterior half of the fossa ovalis (the network is held taut by one cotton thread, 1).

CASE 8—The heart appeared normal. The eustachian valve was a thin, triangular, fenestrated membrane with its base attached to the lower portion of the rim of the inferior vena cava and the inferior sinus septum. Its base was about 2 cm long, and the distance from the middle of the base to the apex, when the membrane was held taut, was about 2 cm. From the apex, a thin thread passed obliquely across the atrium and upward to be inserted on the interatrial septum just above the tuberculum loweri about 1.5 cm posterior to the crista terminalis.



This thread was 3.5 cm long. The thebesian valve was a large thin membrane, covering the orifice of the coronary sinus and attached to its rim by threadlike processes. The orifice and the valve lay in a deep recess beneath the inferior sinus septum, the subeustachian sinus of Keith.

CASE 9—The heart did not play a part in the patient's death and appeared normal. There was a large, delicate, fenestrated and netlike eustachian valve attached to the rim of the inferior vena cava except in its upper portion. The free edge was about 4 cm long and the greatest width was about 1.3 cm. From the upper portion of the valve, two threads were given off close together and ran across the orifice of the inferior vena cava to be attached close together to the tuberculum loweri just above the limbus fossae ovalis. They were about 2 cm



Fig 7 (case 7) —The wall of the right atrium is removed to show an antemortem thrombus formed about the fibers of a reticular eustachian valve.

long. The thebesian valve was a large membrane similar to the eustachian valve, covering the orifice of the coronary sinus.

CASE 10—The heart did not play an important part in the history of this case. A cobweb-like network of thin, delicate fibers in front of the orifice of the inferior vena cava extended partially across the atrium. A thin, narrow membrane represented the usual form of eustachian valve, and the threads of the network were largely attached along the course of this, but, for the most part, they were inserted directly into the rim of the inferior vena cava, anterior to the attachment of the valve (fig 8). In the upper part they were attached to the upper part of the rim of the inferior vena cava, independent of the eustachian valve, which ended considerably below this part. One delicate thread, about 5 cm long, left the anterior edge of the network and ascended to the roof of the atrium, where it was attached

about 1 cm posterior to the crista terminalis. The whole network was flaccid. The thebesian valve was a small, thin, fenestrated semilunar membrane.

CASE 11—A man, aged 40, died suddenly of pulmonary embolism while undergoing examination at the clinic. He had been operated on elsewhere for a strangulated hernia a year before, and had suffered from weakness, abdominal pain, dyspnea and swelling of the legs at night since that time. The clinical examination revealed, besides other things, an indefinite mass in the abdomen, marked edema of the left arm up to the shoulder and edema of both legs. There



Fig 8 (case 10) —The right atrium is opened to show a cobweb-like network in connection with the eustachian valve and a long thread passing from it across the cavity to the roof. *A* indicates the crista terminalis, *B* Chiari's network, *C* the orifice of the inferior vena cava, *D* the eustachian valve, *E* the thebesian valve, and *F* the tricuspid valve.

was a suggestion of acromegaly in an increased prominence of the malar bones and the large square hands. Necropsy revealed massive pulmonary embolism and thrombosis of the left innominate and the subclavian veins, and of the common iliac and the right iliac veins. The hypophysis was enlarged to three times its normal size, and microscopically revealed carcinomatous invasion. A portion of the ileum was black and edematous, with stenosis of the lumen, evidently representing an old healed gangrene of the bowel from the time of the strangulation.

of the hernia. The heart was essentially normal except for the condition in the right atrium (fig 9). Evidence of a eustachian valve or of any remnant of the inferior sinus septum was absent. The orifice of the coronary sinus was 1.3 cm wide in the collapsed state, a thebesian valve was not present. Across the atrial cavity from the region of the orifices of the inferior vena cava and the coronary sinus, several delicate threads passed to an insertion into a wide, flattened and extensive crista terminalis just anterior to the orifice of the superior vena cava.



Fig 9 (case 11) —The right atrium is opened to show the eustachian and the thebesian valves replaced by a Chiari's network (photograph retouched)

There were three main threads, all more than 6 cm long, which were difficult to trace from insertion to insertion because of an entanglement in their median portions. Above, these threads were attached about 1 cm apart, in a row, to the crista terminalis by little cone-shaped bits of endocardium. After leaving the entanglement, which was about 1.5 cm long, they became several small threads, which were attached below to the wall of the atrium in front of and above the orifice of the coronary sinus. Near the end of an unattached thread was a small discoid antemortem thrombus about 0.4 cm in diameter and 0.15 cm thick.

## COMMENT

This series of cases progresses from the more exaggerated forms of the usual type of eustachian and thebesian valves to those in which the valves have been replaced by a number of threadlike processes. Cases 1, 2 and 3 are instances of large fenestrated forms without accessory threads and with the usual ridge representing the remains of the inferior sinus septum. Case 4 illustrates the incomplete separation of the two valves by the inferior sinus septum. Case 5 is an example of a complete failure of the inferior sinus septum, the two valves being one membrane uninterrupted by the muscular ridge. In case 6, the sinus septum was present but failed to cleave the right venous valve into its two definitive valves. The network in the fossa ovalis was a remnant of the left venous valve, which had failed to unite completely with the septum secundum. Case 7 showed a network of threads, one of which passed downward from the eustachian network to connect with the large fenestrated thebesian valve. In case 8, a single strand passed from a much fenestrated anomalous eustachian valve to be attached to the interatrial septum. In case 9, two threads passed from the eustachian valve network to the tuberculum loweri. A single long fiber, 5 cm long, in case 10, left the cobweb-like eustachian valve network, passed across the atrium and was inserted into the roof of the chamber. Case 11 was the most aberrant form of all, both eustachian and thebesian valves being replaced by a number of long threads stretching completely across the atrial cavity from the region of the orifices of the inferior vena cava and the coronary sinus to the upper part of the crista terminalis. In not one of these cases was there any other cardiac anomaly. These last four cases fall readily into the class described by Chiari, since they have threadlike processes formed in association with the venous valves and inserted on remote unnatural parts of the wall of the atrium.

In the main, most authors have agreed on the interpretations of these anomalies of the valves. There are a few cases in which a difference of opinion might exist, but I feel that interpretations of cardiac anomalies are not worth much unless the interpreter has the condition well visualized or has access to the heart itself.

Concerning the cases designated Chiari's network, there are two main conceptions. Chiari concluded that the reticulum is a remnant of the right venous valve and of the septum spurium. Looser believed that it is formed entirely by the right venous valve and a dislocation of the fibers from their normal site by irregularities in the growth of the endocardium. Jordan wished to include the left venous valve as playing a part in the formation of the reticulum. I consider Looser's explanation as the one nearer the truth, preferring to look on all folds or networks formed in association with or replacing the eustachian and the thebesian

valves as remnants of the right venous valve with or without involvement of the inferior sinus septum. Additional evidence for the theory that a dislocation of fibers may occur in the formation of these reticulated structures is the attachment, in some cases, of fibers of the lower part of the network at points in the right atrium far below the lower limit of the right venous valve. This is exemplified best, perhaps, by Chiari's case 10. Spurious threads are seen more rarely in the left atrium, and are probably due to dislocations of remnants formed usually from the septum primum or even the septum secundum. These structures were recently reviewed by Kleine<sup>31</sup>. This conception limits the remnants of the left venous valve to those threads, networks or loose folds at the edge of the fossa ovalis and mainly in the posterior part, instances of the occurrence of which, in a small way, are frequently seen. Remnants of the septum primum are then left as the rarest of all and, so far as I know, are limited to those hearts that show a definite semilunar ridge projecting under the anterior rim of the opening of the superior vena cava at the junction of the anterior and the medial walls of the right atrium. Born is the only author who called special attention to such a ridge, which is seen most often in infants. Anomalies of the sinus septum are also rare as a distinct entity.

This explanation of the origin of Chiari's structure confuses the criteria on which to call a certain reticulum an instance of Chiari's network. Formations of network of the eustachian and the thebesian valves are not uncommon, as shown by the study of the valves in more than 120 hearts. In all of Chiari's cases, however, some of the fibers of the net had their attachment to the atrial wall near the upper portion of the crista terminalis or to the interatrial septum on or near the tuberculum loweri. Therefore, the term, Chiari's network, should probably be applied only to reticular formations that possess such threads.

Clinically, these reticula are usually not of consequence. Instances are on record, however, in which thrombi were found in the reticulum. Five of these have already been noted from the literature, and in Chiari's case 1 such a thrombus apparently caused the death of the patient from pulmonary embolism. Also, in case 11 (fig 9) of the present series, the patient died of pulmonary embolism, but there was extensive thrombosis of several large veins, as well as the thrombus attached to the network. In case 7 (fig 7) there was an embolus in the left pulmonary artery, although the patient did not die of pulmonary embolism. The large thrombus surrounding the threads of the eustachian valve was the only source found for the embolus. In another case (not recorded

31 Kleine, H. O. Zur Morphologie der Missbildungen des linken Vorhofs (Chorda tendinea spuria atrii sinistri), Virchows Arch f. path. Anat. **267**: 281, 1928.

here), the patient died of septicemia following an induced abortion. She had had dyspnea for two years. At necropsy, a large egg-shaped fibromyxoma was found attached to the wall of the left atrium and filling it, on a thread of the eustachian valve was a large recent thrombus. In a fourth case (not recorded here), there were antemortem thrombi on several threads of the thebesian valve. These long threadlike processes hanging limp in the cavity of the right atrium and being whipped about by the blood current must form excellent bases for the formation of thrombi, when the rate of circulation is depressed or the condition of the blood becomes favorable for clotting. That they are whipped about vigorously is shown by cases 7 and 11, in which the threads were so entwined and entangled as to be inseparable for some distance. In Haas' case, instead of being the source of pulmonary embolism, however, the network prevented such a condition by catching a large embolus in its course from the inferior vena cava to the pulmonary artery. The reticulum in one of Thilo's cases may have played a similar rôle, but because of the uncertainty of this I have included it as an instance of the formation of a thrombus in situ.

Case 4 of this series illustrates the possible mechanism by which circus movement may ensue in isolated instances. The cardiac muscle bands in the large valvular fold joined with the muscle of the atrium at each end of the fold and thus formed a circuit of muscle about the mouth of the inferior vena cava. The patient had auricular flutter, and it is conceivable that the main path of the contraction wave was this ring of aberrant muscle.

#### SUMMARY

Several varieties of remnants of the venous valves of the embryo occur. There are two main groups of anomalies, those with and those without defective interatrial septums. I have described those without a defective septum.

The literature contains reports of twenty-two acceptable examples of that anomaly known as Chiari's network, including Chiari's original eleven cases. To these I have added four more. The designation, Chiari's network, should be confined, probably, to those reticula in connection with the eustachian and the thebesian valves which have threads attached in the upper region of the atrium, near the crista terminalis, or to the interatrial septum in the region of the tuberculum loweri.

Such reticular formations as have been described are usually not of clinical significance. In a certain number, however, an increased facility for the formation of thrombi on the threads of the network is noted. In the literature, five instances are recorded in which such thrombi were

present, and in one there was no doubt that the thrombus was the cause of fatal pulmonary embolism. In this series were four cases in which thrombi were found in connection with the eustachian or the thebesian valve, all apparently antemortem thrombi. It is possible for a person to succumb to pulmonary embolism the source of which is a thrombus formed on one of these networks. Paradoxically, such a network, by ensnaring an embolus from some vein, may prevent fatal pulmonary embolism.

A theoretical point to be considered is the possible relationship of these networks to auricular fibrillation or auricular flutter.

# LEUKOCHLOROMA IN THE COMMON FOWL

ITS RELATION TO MYELOGENIC LEUKEMIA AND ITS ANALOGIES TO  
CHLOROMA IN MAN

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Among the early reports in the literature on the occurrence of a myeloid neoplasm in the common fowl are those published in 1908 by Ellerman and Bang<sup>1</sup>. Their studies at that time were concerned chiefly with efforts to transmit the disease and not with its microscopic changes. From 1915 to 1916, Schmeisser<sup>2</sup> conducted similar transmission experiments with a tumor that was evidently of myelogenous origin. In 1915, Pentimalli<sup>3</sup> published a brief description of two cases of neoplastic growths that he classified as myelocytomas. The first occurred in a hen into which he had transplanted a chondroma. He apparently considered that there had been a "transformation" of the chondroma into the myelocytoma. This explanation did not obtain for the second case.

The myeloid neoplasm in man, commonly known as a chloroma, has been the subject of considerable study. Burns<sup>4</sup> (1823) is credited with making the first observations on it. Dock<sup>5</sup> presented evidence of a relationship between the tumor and leukemia. Dock and Warthin<sup>6</sup> established this point, and called attention to the fact that the bone marrow is the seat of the primary development. In 1910, Lehdorff<sup>7</sup> reviewed the reports of seventy-three cases. From the evidence presented, he classified fifty-six as lymphogenic and seventeen as myelogenous.

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1 Ellerman, V., and Bang, O. Experimentelle Leukämie bei Hühnern, Centralbl. f. Bakteriologie **46** 4, 595 and 609, 1908.

2 Schmeisser, H. C. Spontaneous and Experimental Leukemia in the Fowl, J. Exper. Med. **22** 820, 1915, Leukemia of the Fowl, Spontaneous and Experimental, Johns Hopkins Hosp. Rep. **17** 551, 1916.

3 Pentimalli, F. Ueber die Geschwulste bei Hühnern, Ztschr. f. Krebsforsch. **15-16** 111, 1915-1919.

4 Burns, A. Observations on the Surgical Anatomy of the Head and Neck, Baltimore, 1823, p. 386.

5 Dock, G. Chloroma and Its Relationship to Leukemia, J. M. Sc. **106** 152, 1893.

6 Dock, G., and Warthin, A. S. A New Case of Chloroma with Leukemia, with a Study of Cases Reported Since 1893, Med. News **85** 971, 1904.

7 Lehdorff, H. Chloroma, Ergebn. d. inn. Med. u. Kinderh. **6** 221, 1910.



The subject was reviewed by Bugess,<sup>8</sup> in 1912, who presented logical reasons for considering the neoplasm as a myelogenic process, and also called attention to the fact that a thorough histologic study had not been conducted on the majority of the growths that had been classified as lymphogenic chloromas. Brannan<sup>9</sup> reviewed seventy-four cases that were reported from 1910 to 1925, of which forty-nine were definitely myeloid in nature. He emphasized the fact that the better studied cases of chloroma had been shown to be of myelogenic origin. Other recent accounts of the disease, with appended bibliographies, can be found in the articles by Boots,<sup>10</sup> Rowe and Hirschboeck<sup>11</sup> and Goodall and Alexander.<sup>12</sup>

Observations by members of the Veterinary Department of Purdue University have shown that from the standpoint of incidence in the common fowl the myeloid tumors rank second in importance to the lymphocytomas. The nature of the lymphocytoma has been thoroughly studied, whereas the myeloid tumors have received but slight attention from the comparative pathologist. The present publication deals with thirty-seven myeloid neoplasms that I studied during the years 1925 to 1928.

#### SYMPTOMS

The clinical manifestations in most cases were a slight indisposition, lasting not to exceed a week, a diarrhea in the terminal stages and the refusal of food for two or three days before death. Sudden death without noticeable symptoms was occasionally observed. More striking, although not characteristic of the disease, were the symptoms of a transverse myelitis, the birds with this disorder were prostrated and showed a twitching of the limbs, which were in a constant state of extension. A palpation of the sternum, in many cases, disclosed a bilateral tumor-like induration along the keel bone. A history of an occasional death in the flock was generally obtained.

#### ENZOOLOGY

As a rule, the disease occurred sporadically in birds less than 1 year of age. It was most prevalent during the months of November, December and January, seldom was a case observed during the other nine months of the year. Two enzootic outbreaks were observed that sug-

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8 Burgess, A. M. Chloroma, *J. M. Research* **27** 133, 1912.

9 Brannan, D. Chloroma. The Recent Literature and a Case Report, *Bull. Johns Hopkins Hosp.* **38** 189, 1926.

10 Boots, R. H. Chloroma. With Report of a Case, *J. Lab. & Clin. Med.* **2** 622, 1916-1917.

11 Rowe, O. W., and Hirschboeck, F. J. A Case of Myeloid Chloroma, *Am. J. Dis. Child.* **24** 239 (Sept.) 1922.

12 Goodall, A., and Alexander, W. A. Acute Myelocythemia and Chloroma, *Quart. J. Med.* **17** 113, 1923-1924.

gested a potential economic aspect of the disease. The flocks concerned in the two outbreaks were small, totaling about sixty birds each. There was a mortality of 20 per cent in the first and a mortality of 10 per cent in the second flock during the months of November and December. In neither case were data of mortality obtained for the month of January, as the first flock was sold in the early part of that month and the owner of the second flock lost interest in the situation after receiving the same diagnosis on four separate occasions. Autopsies were not conducted on all the birds that died in the two flocks, but, at irregular intervals during the months of November and December, the owners presented birds to the laboratory for postmortem examination. In all the necropsies, the gross and microscopic pictures were of the neoplasm under discussion, and since all suggestions of a second disease were absent, it was assumed that the losses in these cases were due to the leukochloroma.

Twenty flocks were represented in the thirty-seven cases studied. The original source of six of these flocks was a flock in which annual,

TABLE 1—*The Annual Incidence of Leukochloroma*

Periods of Observation	Number of Cases	Number of Birds Examined Postmortem	Incidence, per Cent
1925	3	595	0.5
1926	5	848	0.6
1927	11	1,177	0.9
1928	17	1,318	1.3

sporadic outbreaks of the disease were known to occur. The ancestry of three other flocks was probably the same, although this was not definitely shown. The ancestry of the remaining eleven flocks was not determined.

Table 1 gives the incidence of the disease as it was observed from year to year. In the year ending in June, 1925, an incidence of 0.5 per cent was observed and, with each subsequent year, an increased incidence was observed, the highest point, 1.3 per cent, being reached in the year ending in June, 1928.

The neoplasm was conspicuously present in Barred Rocks, although not confined to this breed, two cases having been observed in White Leghorns and a third in a White Rock. The majority of the cases occurred in females, an incidence that was undoubtedly influenced by market conditions, since most of the males had been disposed of as broilers before reaching the age at which the tumor, if present, usually destroys its host.

#### MORBID ANATOMY

The carcasses were those of well nourished fowls, and the amount of subcutaneous and visceral fat was frequently excessive. Emaciation was not encountered.

**The Neoplastic Growth** Regardless of its location, the tumor presented a characteristic appearance. It was devoid of pigment, having the chalky-white, bloodless look that distinguishes it from the other common tumors of the fowl. It was exceedingly friable, disintegrating readily on slight manipulation. Necrotic areas were seldom seen, in spite of the fact that the pallid appearance suggested a scanty supply of blood.

**Sternum** The point of union between the xiphoid cartilage and the keel bone was constantly the location for the tumor's development. Sometimes an incision of the muscle of the breast was required before the new growth could be revealed, but in the majority of cases there was an easily recognizable swelling at this point. In the well advanced cases, the tumor was from 2 to 3 cm. in thickness, and on examination was found to be an outgrowth from a much rarefied bone. The characteristic growth was also found with remarkable regularity on the internal aspect of the body of the sternum.

**Ribs** An irregular chain of nodules or a cylindroid growth was usually found along the borders of the ribs. The periosteum of the ribs, as well as that of the sternum and the spinal column, was frequently intact, but was separated from the

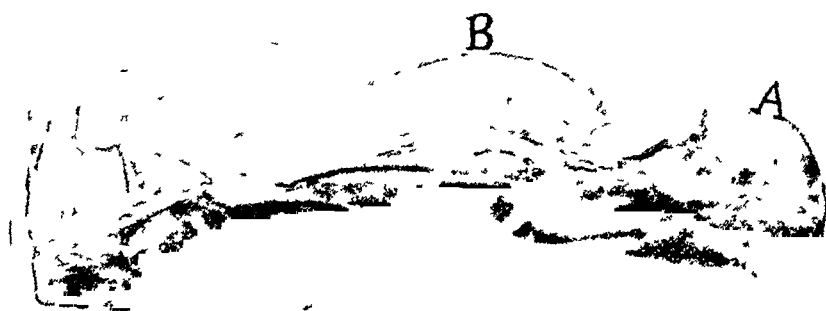


Fig 1—A primary leukochloroma involving the xiphoid cartilage, *A*, and a second and larger tumor located anterior to the first, *B*.

bone by the neoplastic growth. In many locations, the periosteum was infiltrated to such an extent that its gross identity was lost. Many of the bones, and especially the ribs, had a bleached appearance on account of the tumor's having replaced much of the red bone-marrow.

**Spinal Column** In about 50 per cent of the cases, a neoplastic process involved the spinal column from about the middle of the thoracic region to as far back as the coccygeal vertebrae. The bodies of the vertebrae were sometimes dotted with the tumors, and sometimes their ventral surfaces were covered with a neoplastic mass that varied from 1 to 2 cm. in thickness. The bones were rarefied to a marked degree, and the new growth extended through the bodies of the vertebrae and into the spinal canal. The spine was easily fractured and offered but slight resistance when cut with a knife. The extension of the tumor into the spinal canal resulted in pressure on the spinal cord, a condition that explains most of the symptoms of transverse myelitis.

**Spleen** The spleen, in some cases, was slightly enlarged, and in others it was increased to several times the normal volume. Occasionally, the organ had a

mottled appearance due to the formation of white, circumscribed tumors beneath the capsule, as a rule, however, the normal color was but slightly altered

**Liver** The liver, in about 65 per cent of the cases, showed gross evidence of metastases The metastases varied all the way from a few circumscribed foci to



Fig 2—*A*, neoplastic nodules along the borders of the ribs, *B*, extensive ovarian involvement, and a large tumor posterior to the ovary

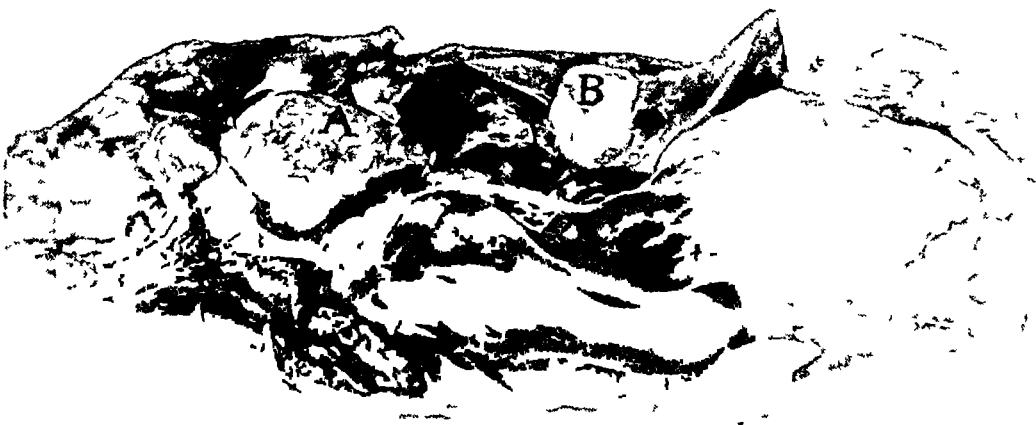


Fig 3—Metastatic leukochloroma, *A*, in the heart, *B*, in the liver

a diffuse neoplastic growth that displaced most of the parenchymatous tissue In the advanced cases, the liver was slightly enlarged, and it was not infrequently found ruptured

**Ovary** In the majority of cases, the ovary revealed an extensive neoplastic development. The organ was chalky-white and studded with an occasional atrophic graafian follicle.

**Kidneys** Metastatic tumors were found in the kidneys with less frequency than in the liver or the ovary. When present, the white neoplasm stood out in bold relief against the maroon background of the parenchyma.

**Intestine and Pancreas** The small intestine, especially the upper part of the duodenum, was frequently involved. In advanced cases, the walls of the intestines in numerous areas had been displaced by new growth. The marked intestinal

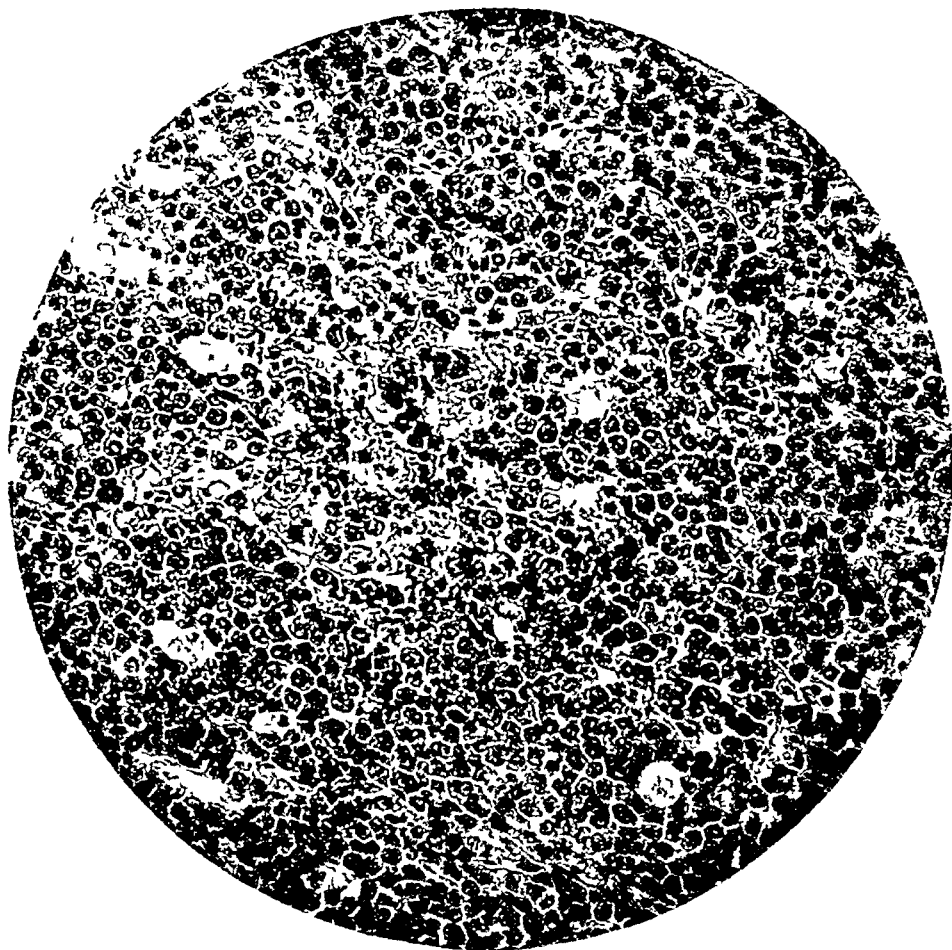


Fig 4—A section of the liver showing the parenchyma practically displaced by myelocytic cells

involvement was generally associated with sharply circumscribed tumors of the pancreas.

**Heart** In some cases, the epicardium was slightly elevated by new growths that extended into the myocardium to a variable depth. Similar growths occurred in the endocardium. The parietal pericardium was seldom involved.

**Lymph Glands** The lymph glands were enlarged and in some instances showed nodular, neoplastic development.

**Other Organs** Metastatic tumors were frequently found in the lungs. Unusual locations in which metastases occurred were the sciatic nerve, the esophagus, the gizzard, the trachea and the thyroid gland. The bones of the head showed a marked involvement in two cases.

## MICROSCOPIC CHANGES

**The Neoplastic Growth** The tumor proper had an extremely cellular make-up. The cells were spherical, unless distorted by pressure, and were about equal in size to the mature avian myelocyte. Each cell had an eccentrically located, round or oval nucleus occupying about one half of the cellular space. Multinucleated cells were seldom found. The chromatin was disposed in the form of a fine reticulum, which appeared to radiate from a single nucleolus. Rapid growth was evidenced by an abundance of mitotic figures. In some cases, as many as twelve cells undergoing mitotic division were counted in a single field (4 mm objective). The cyto-

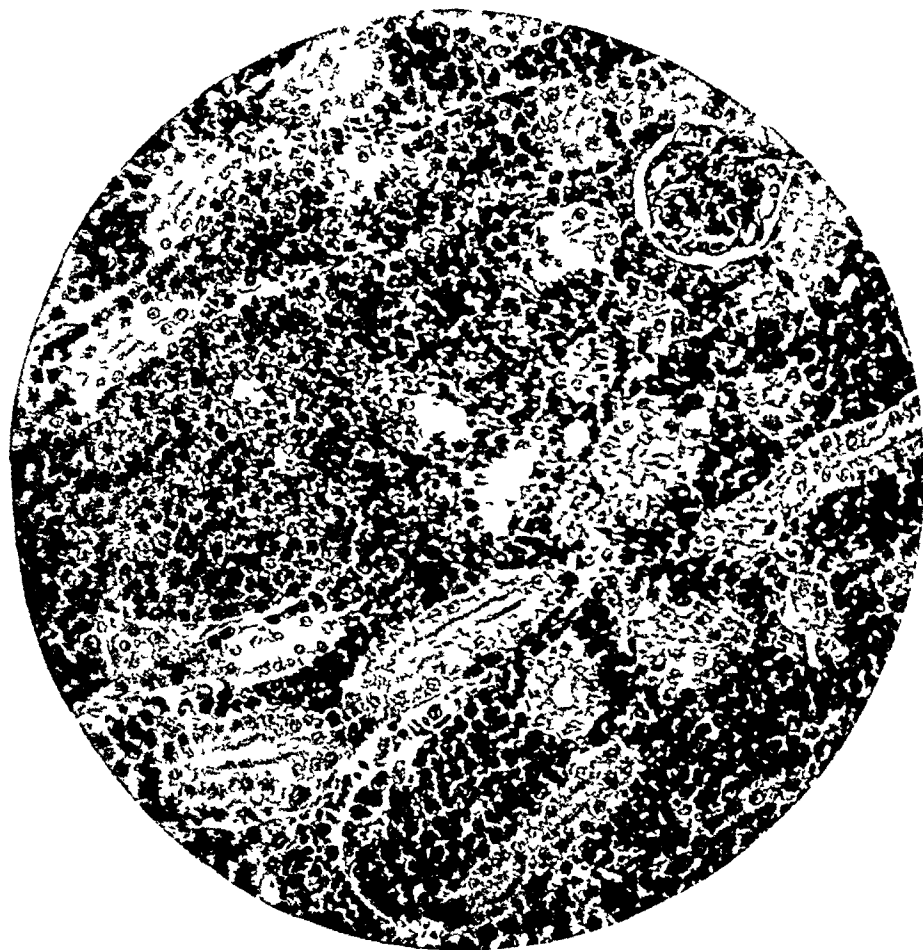


Fig 5—Myelocytic cells infiltrating between the kidney tubules

plasm had a definite outline, and was filled with numerous spindle-shaped granules, which took a brilliant eosin stain. The granules were of the same size and shape as those found in the mature myelocyte or the crystalloid polymorphonuclear leukocyte. The stroma consisted of a scanty reticulum, which gave the connective tissue reaction when stained by van Gieson's method. The supply of blood was more abundant than was suggested by the gross appearance.

**Liver** On microscopic examination, the liver was found to be constantly the location for metastatic tumors. In the early cases, i e, the cases in which gross evidence of an involvement of the liver was not observed, the neoplastic cells had a periportal distribution. In the well advanced cases, a diffuse infiltration and

filling of the sinusoidal spaces with myelocytic cells had resulted in the destruction of much of the normal parenchyma

**Spleen** The spleen presented the picture of a lymphoid exhaustion. In some cases, the splenic nodules were moderately engaged in the production of lymphocytes, but, as a rule, evidence was lacking that these structures had been recently engaged in the fulfilment of their normal function. There was a pronounced infiltration with myelocytic cells, which were found principally in the pulp and not in the splenic corpuscles. The infiltration of the pulp accounted for the splenic enlargement.

**Kidney** One or both kidneys frequently showed numerous areas in which myelocytic cells had infiltrated the interstitial tissue. The epithelium of the

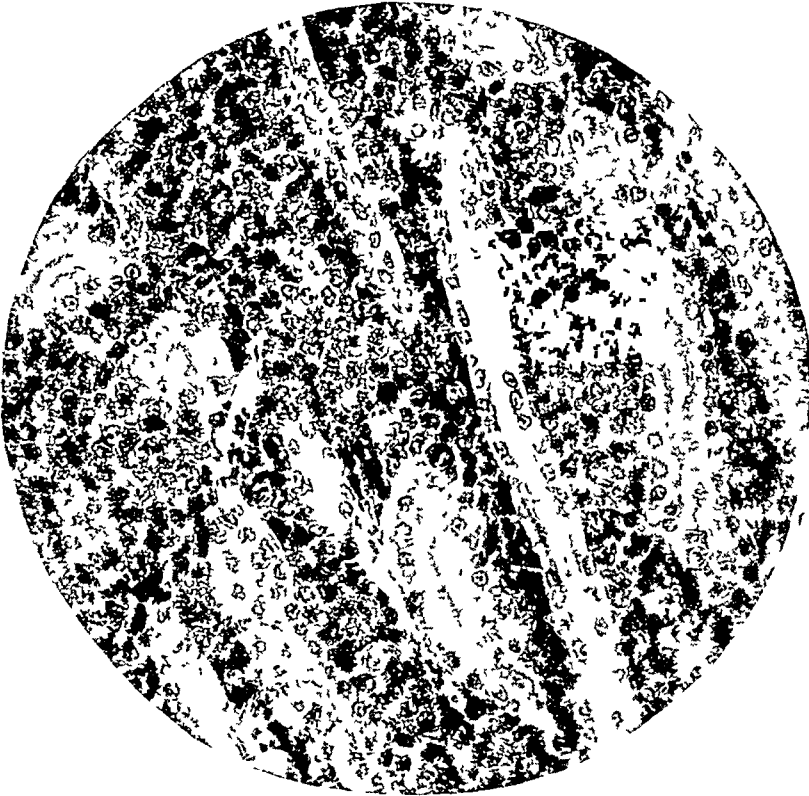


Fig 6—Metastatic leukochloroma in the kidney. The parenchyma shows moderate retrogressive changes.

tubules within the infiltrated areas showed considerable atrophy and fatty infiltrative degeneration, but not the pronounced necrosis that generally accompanies the infiltration of parenchymatous organs by some of the other types of malignant neoplasms. For the most part, pronounced necrotic changes did not accompany the infiltration of normal tissues by this type of tumor.

**Ovary** The stroma showed a marked myelocytic infiltration. The graafian follicles were atrophic and few in number. The follicular epithelium was frequently pyknotic, and occasionally cells of myelocytic type were found floating in the liquor folliculi.

**Intestine** The submucosa appeared to be the seat of metastases in the intestine. From this location, the infiltration progressed toward the lumen and the periphery until the epithelium was denuded and much of the muscular wall was displaced by the tumor.

**Heart** Metastases in the heart occurred just beneath the epicardium and the endocardium. From these locations, finger-like processes infiltrated between the myocardial cells. The extent of the lesions suggested that metastases in the heart do not occur until late in the disease.

**Bone-Marrow** Sections of bone taken from any part of the skeleton showed at least some neoplasm-like hyperplasia of the marrow. In many places, the normal constituents of the marrow were entirely replaced by mature myelocytes. The tumor, which in the gross appeared to be exuding from the bones, was found, in many cases, to be proliferating beneath the periosteum. In other cases, the periosteum was practically destroyed by neoplastic infiltration, but enough of



Fig 7—A section of myocardium showing a subepicardial tumor and an infiltration into the myocardium

the normal tissue still existed to show that its normal relation to the bone had been lost. Cords of cells that connect the subperiosteal tumors with the neoplastic bone-marrow were easily demonstrated.

**Blood** Fixed tissues prepared for microscopic examination, with one exception, showed the presence of numerous mature myelocytes in the blood vessels, and it was not uncommon to find cells of this type undergoing mitotic division within the blood stream. From these observations it was evident that a myelocythemia existed in most cases. Differential and total leukocyte counts were made on the blood of seven fowls, the results of which are given in table 2. A definite leukemia was found in all but one case (no 220), and there was a high eosinophil count in this case. In preparing smears for differential counts, it was found that the eosinophil cells underwent a rapid degeneration, so that it was impossible to



differentiate between myelocytes and polymorphonuclear leukocytes. For this reason, all eosinophil cells were grouped under one heading. In six of the cases, there was a high eosinophil count, in the seventh, which is of special interest and will be discussed later, there was a marked lymphatic leukemia.

#### EXPERIMENTAL TRANSMISSION

Twenty-three fowls were inoculated with material from the tumors in three spontaneous cases.

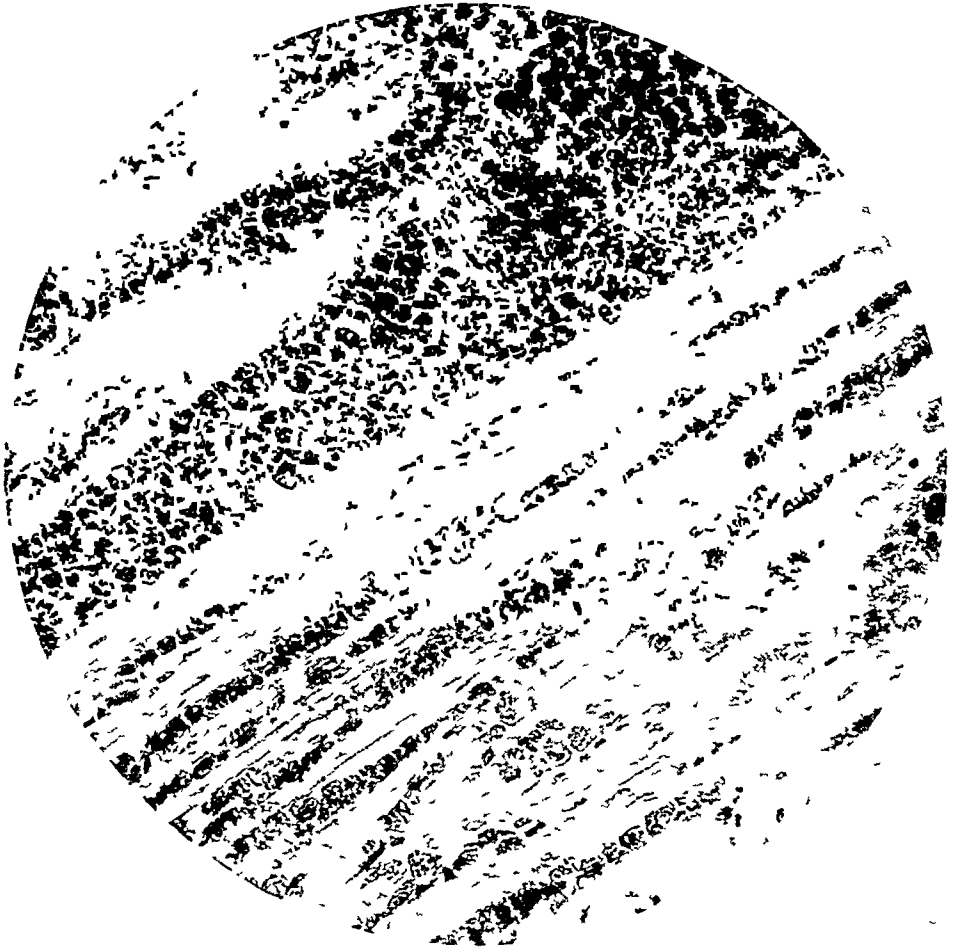


Fig 8—A higher magnification of figure 7

The material was intraperitoneally transplanted into 12 and subcutaneously transplanted into 2. For 4, the inoculum was macerated in physiologic sodium chloride solution and injected intraperitoneally, the same inoculum was injected subperiosteally into 2. Large amounts of the inoculum were fed to 3 birds. The inoculations were completed within thirty minutes from the time that death occurred in the spontaneous cases. Five of the birds used for the experimental work were crosses of Barred Rock and Rhode Island Red, the remainder were White Leghorns. At the time of their inoculations the birds were from 2 to 12 weeks of age. At intervals ranging from three months to one year after the inoculations, the fowls were killed and autopsies made on them.

In not a case was there evidence, either gross or microscopic, that the disease was infectious and had been reproduced experimentally in these birds

#### COMMENT

A few conspicuous features of the chloroma of man are absent or of minor importance in the leukochloroma of the fowl. The green color has not been observed in the neoplasm in the fowl. However, this factor in chloroma can hardly be considered an essential part of the pathologic process, since both green and colorless tumors have been encountered in the same patient. Exophthalmia has not been observed in the disease in chickens. A predilection for the bones of the head has been noted in but two cases.

With the foregoing exceptions, the two tumors possess sufficient characteristics in common to warrant an assumption that one is dealing with the same disease in both species. Tumorous development resulting

TABLE 2—*Total and Differential Leukocytic Counts in Seven Cases of Leukochloroma of Fowls*

Case	Total White Cells	Eosinophil Cells	Lymphocytes	Large Mononuclears
1	12,800	77	22	1
2	40,000	89	8	3
3	60,000	88	12	0
4	42,000	65	31	4
5	60,000	88	7	5
6	49,000	18	80	2
7	125,000	90	9	1

in a rarefaction of the sternum, the ribs and the spinal column is a characteristic manifestation of the disease in both man and fowl. Early metastases, especially to the liver, with no part of the body exempt, and an enlargement of the spleen and the lymph nodes without definite formation of a tumor are characteristics of the neoplasm in both species. The disease runs a rapid, fatal course, is frequently accompanied by neurologic symptoms and, as a rule, occurs during early life.

Histologically, the neoplasm in both species consists essentially of myeloid cells supported by a scanty reticulum of connective tissue and a supply of blood that is sufficiently adequate to prevent any pronounced necrosis. The important histologic changes in chloroma in man, which were shown by Dock and Warthin to consist of a tumor-like hyperplasia of the bone marrow, an enlargement of the marrow spaces, a rarefaction of the bone trabeculae and a direct extension of the neoplasm from the marrow spaces to the periosteum and surrounding structures, are found to be the essential pathologic changes in leukochloroma. Since the important histologic changes are found in the bones in both species, the disease should be considered a primary neo-

plastic overgrowth of the bone-marrow with direct extension to the periosteum and secondary metastases to other parts of the body. Wide-spread metastases that exhibit a rapid, diffuse infiltration into the normal structures are a constant part of the pathologic picture.

The leukemic stage of the disease in man is generally myelogenic in nature, at least to some extent. The presence of mature myelocytes in the blood vessels of fixed tissues indicates that the terminal stage of the disease in chickens is accompanied by a myelogenic leukemia.

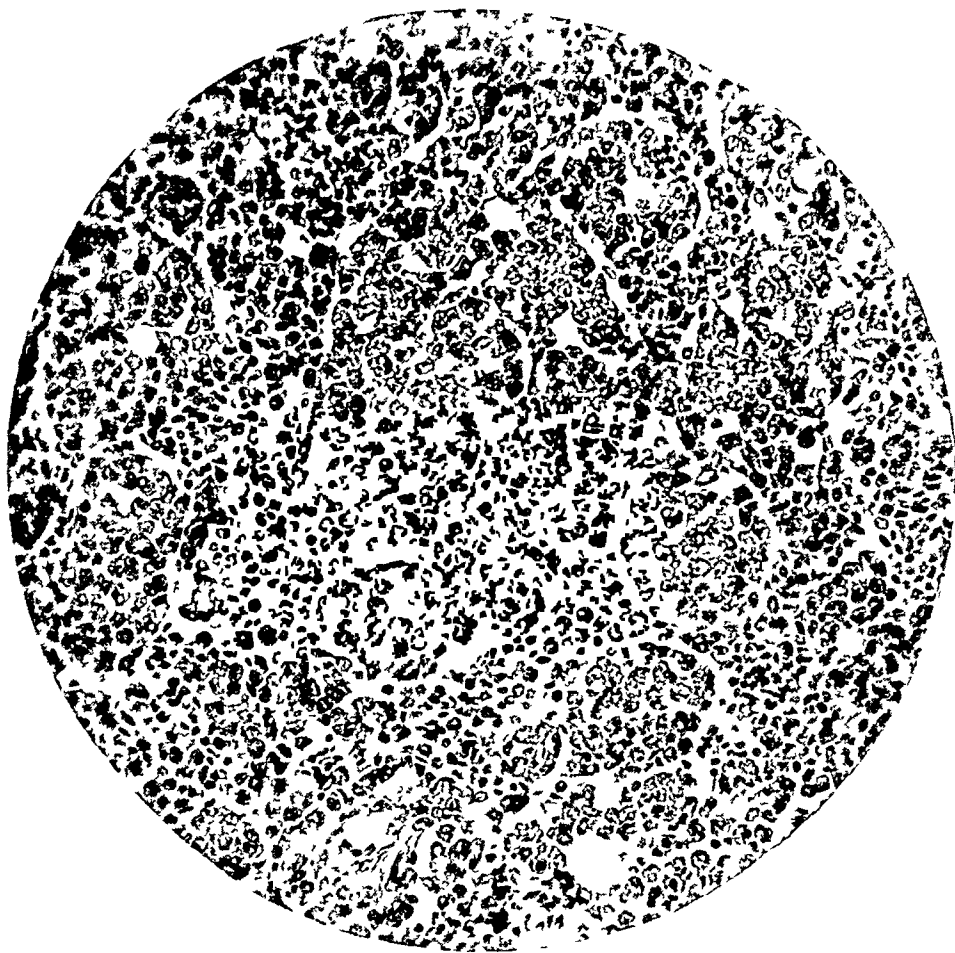


Fig 9—A section of bone-marrow showing the fat cells and other constituents of the marrow displaced by tumor cells

Further evidence of a secondary leukemia is to be had in the differential leukocytic counts in six typical cases, in all of which there was a high percentage of eosinophil cells, and in five high white cell counts. Later, the examination of fixed tissues from these cases proved that the predominating white cells in the blood vessels were mature myelocytes. A secondary leukemia is therefore part of the syndrome in both species. An aleukemic stage of the disease in the fowl has not yet been demonstrated.

The experimental inoculations previously described were not of sufficient numbers to enable one to draw conclusions either for or against the infectious nature of the disease. They do not, however, support the observations of Ellerman and Bang,<sup>1</sup> Elleiman<sup>13</sup> and Schmeisser.<sup>2</sup> Ellerman and Bang observed myeloid responses following lymphoid inoculation and vice versa. From these results, they concluded that the two conditions were different manifestations of the same disease, and were caused by the same infectious agent. The frequency

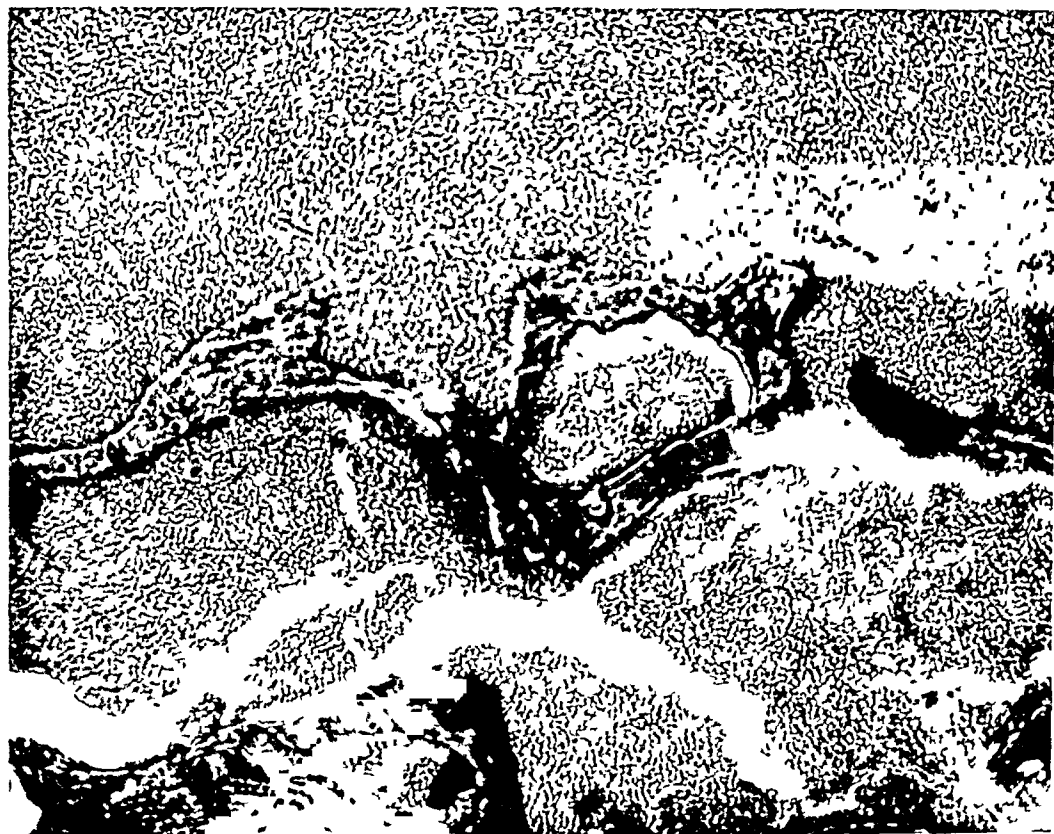


Fig 10—A section of bone showing enlarged marrow spaces. The neoplastic outgrowth has destroyed the normal relation of the periosteum to the bone.

with which lymphocytomas and leukochloromas are encountered in chickens and the fact that these two neoplasms are found much more frequently in some flocks than in others should prompt one to caution in interpreting experimental results of this nature. Research dealing with the etiology of the leukemias in fowls should be preceded by a thorough tracing of the ancestry of the birds to be used in the experimental work. Schmeisser frequently observed an icteric condition about

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13 Ellerman, V. A New Strain of Transmissible Leukemia in Fowls, *J Exper Med* 33 539, 1919.

the head, and a fibrinous pericarditis in his experimentally produced leukemias. These pathologic results are more suggestive of fowl typhoid than of either of the neoplastic leukemias. These observations, associated with the fact that he considered 80,000 leukocytes per cubic millimeter of blood to be within the normal limits for the fowl, lead one to suspect that more than one etiologic factor was operating in his experiments.

Winternitz and Schmeisser<sup>14</sup> noted myeloid infiltrations and proliferations in the liver, the spleen and the lymph glands of birds inoculated with material containing the organism of fowl typhoid, and from these and other pathologic results, concluded that they had produced "presumptive evidence" of a relationship between fowl typhoid and the neoplastic leukemias. Here, again, one finds it difficult to accept the evidence on account of the fact that myeloid changes, if present in the liver, are not a conspicuous part of the syndrome of fowl typhoid. We must therefore conclude at the present writing that the etiologic factor in the neoplastic leukemias of fowls has not been proved to be of an infectious nature.

Other investigators have considered the myeloid and the lymphoid neoplasms of fowls to be different manifestations of the same disease. This theory is not supported by my observations, although, during the past four years, I have made both gross and microscopic studies of 136 cases that were similar, in most respects, to the cases of lymphocytoma described by Warthin,<sup>15</sup> and by Tyzzer and Ordway.<sup>16</sup> The lymphocytoma presents, both grossly and microscopically, characteristics differing materially from those of leukochloroma. The former condition is commonly associated with emaciation and occurs in birds of all ages, whereas the latter usually occurs in well nourished birds less than 1 year of age. The lymphocytoma is gray. It is frequently associated with a profound enlargement of the liver. Although occurring in the bones, it does not produce the rarefaction and the neoplastic outgrowth into the periosteum and surrounding structures that characterize the leukochloroma. The bones in leukochloroma have a bleached appearance and are easily fractured, whereas, in lymphocytoma, the skeleton retains its normal rigidity. The leukochloroma has a characteristic chalky-white appearance. It is not associated with a profound enlargement of the liver. Not infrequently, one finds either the liver or the ovary showing a well advanced lymphocytoma with the other organs

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<sup>14</sup> Winternitz, M. E., and Schmeisser, H. C. Studies on the Relation of Fowl Typhoid to Leukemia of the Fowl, *Johns Hopkins Hosp. Rep.* **18** 25, 1919.

<sup>15</sup> Warthin, A. S. Leukemia of the Common Fowl, *J. Infect. Dis.* **4** 369, 1907.

<sup>16</sup> Tyzzer, E. E., and Ordway, T. Tumors in the Common Fowl, *J. M. Research* **21** 459, 1909.

not involved, so far as can be determined. Metastasis to other organs of the body is invariably preceded by an involvement of the bone marrow in leukochloroma.

Microscopically, the lymphocytoma is composed of cells resembling either the large or the small lymphocytes, the large myeloid cells are not encountered. The leukochloroma is characterized by large eosinophil myelocytes which do not in any way resemble the lymphocyte. Both diseases are associated with leukemia, but in the former the leukemia is lymphatic and in the latter it is myelogenic.

From the foregoing observations, it is evident that the two diseases are much more readily differentiated on a pathologic basis than are some of the more common diseases that are known to be of infectious origin. By reason of this, it appears to me that the lymphocytoma and the leukochloroma should be considered as two disease entities.

In view of the frequent occurrence of the two diseases, it is not surprising that both should be encountered in one and the same subject, especially if the diseases are later proved to be of an infectious nature. There was one fowl in the present series (previously mentioned) that showed a pronounced lymphatic leukemia. On autopsy, this fowl presented all the characteristic features of a lymphocytoma, and the presence of leukochloroma was not detected until a microscopic examination was conducted. In this case, the liver was found containing both lymphocytomas and leukochloromas. In some fields, the two types of cells were mixed, in other fields, the neoplasms were either purely lymphocytic or purely myelocytic. In addition to those in the liver, metastatic tumors were found in the gizzard, the ovary, the lungs and the kidneys. With the exception of the tumors in the liver, every one of the secondary neoplasms was entirely lymphocytic, and, in view of the evidence presented, this case was diagnosed as an advanced lymphocytoma with an early developing leukochloroma.

As previously stated, the disease is much more prevalent during November, December and January than at any other time of the year, and occurs, for the most part, in birds less than 1 year of age. It will be noticed that the seasonal occurrence follows by approximately from eight to eleven months, the three months of greatest activity on the part of the commercial hatcheries. Evidently, the age of greatest susceptibility accounts for its seasonal occurrence.

The fact that 30 per cent of the flocks concerned in the present investigation were found to have a common ancestry suggests that a hereditary factor is associated with the occurrence of the disease. The common ancestry in this case was a breed of Barred Rocks which is maintained on the same premises with other breeds of chickens, and although the disease makes an annual appearance, it is confined exclusively to the one breed. The occurrence of lymphocytoma has

also been found unusually prevalent in certain strains of fowls. Such evidence of heredity, although far from conclusive, is in keeping with the observations of Slye,<sup>17</sup> who stated that the occurrence of leukemia, pseudoleukemia, lymphosarcoma and kindred diseases has "followed the laws of heredity as surely as have neoplastic diseases." In other words, susceptibility to the neoplastic leukemias is regarded by her as an inherited mendelian recessive characteristic. It is this possibility of a hereditary factor which necessitates a thorough knowledge of the ancestry of the birds to be used, before experimental work on the neoplastic leukemias of the fowl is undertaken.

#### CONCLUSIONS

The common fowl is subject to a myeloid neoplasm that is associated with myelogenous leukemia. As a rule, the disease occurs sporadically in birds less than 1 year of age, but it may become enzootic. Analogies to the chloroma of man suggest the name leukochloroma.

The disease is analogous to chloroma in that it is a primary neoplastic hyperplasia of the bone-marrow with direct extension to the periosteum. The sternum, ribs and spinal column are common locations for the primary development. Metastases to all parts of the body are of frequent occurrence. The neoplasm is composed of myelocytes supported by a scanty connective tissue reticulum. There is a secondary myelogenous leukemia. The disease is most prevalent in the young. It runs a rapid, fatal course.

The etiologic factor in the disease has not been proved to be of an infectious nature.

The leukochloroma differs from the lymphocytoma of fowls in that the former is a disease of young birds. The bone-marrow is the seat of the primary development, which results in a rarefaction of the bones. The neoplasm is chalky-white. It is made up of mature myelocytes. The disease is associated with myelogenous leukemia. The lymphocytoma occurs in birds of all ages. It is gray. It does not produce a rarefaction of the bones. The neoplasm is composed of lymphocytes and is associated with lymphatic leukemia. On account of these features differentiating the two neoplasms, they should be considered as different disease entities.

There is evidence of an hereditary susceptibility to the neoplastic leukemias in mice. The evidence suggests that heredity is associated with the occurrence of leukochloroma.

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<sup>17</sup> Slye, Maude. Cancer and Heredity, *Ann Int Med* 1 951, 1928.

# THE ARTERIAL SUPPLY OF THE KIDNEY IN NEPHRITIS

ITS RELATION TO THE CLINICAL PICTURE <sup>1</sup>

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In the primary contracted kidney, progressive sclerotic thickening of the walls of the arterioles and narrowing of the lumen are considered adequate to explain the fibrosis and the shrinkage of the organ. Between the scattered areas of ischemic sclerosis and atrophy lie other areas of normal parenchyma, which may continue to meet the demands of urinary excretion until the kidney has contracted to an exceedingly small size. Before this reduction in size of the organ reaches a point incompatible with life, the prolonged strain of maintaining an arterial hypertension and the vascular changes in the myocardium often result in cardiac decompensation. It is therefore often not alone the reduction in normal secreting parenchyma but the additional burden of circulatory embarrassment that precipitates the renal insufficiency.

In still other instances, the end stages of the primary vascular disease are accelerated by the rapid development of necrosis and of inflammatory lesions in the walls of arterioles and small arteries throughout the kidney—the so-called malignant sclerosis of Fahr<sup>1</sup> or malignant hypertension of Volhard. This soon determines the onset of renal insufficiency and azotemia.

In chronic diffuse nephritis (the secondary contracted kidney), a primary glomerular damage initiates the pathologic process, although the tubules and the interstitial tissue are also always more or less involved. The subsequent sclerosis and contraction of the organ is generally ascribed to this diffuse disease. Although attention has been called by Loehlein,<sup>2</sup> Volhard,<sup>3</sup> Fahr,<sup>4</sup> Branch and Linder<sup>5</sup> and, most

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\* From the Mount Sinai Hospital

† Read before the American Association of Pathologists and Bacteriologists, May 2, 1928

1 Fahr Ueber Nephrosclerose, Virchows Arch f path Anat **226** 119, 1919  
Henke and Lubarsch Handbuch der speziellen pathologischen Anatomie und Histologie **6** 405, 1927

2 Loehlein Ueber die enzueendlichen Veraenderungen der Glomeruli, Leipzig, S Hirzel, 1906



recently, Fishberg<sup>6</sup> to the sclerosis of arterioles and small arteries in chronic diffuse nephritis, few clinicians have appreciated how characteristic and widespread are secondary arteriolar lesions in this disease

Fishberg pointed out that the lesions of the vessels are essentially an endarteritis obliterans. He therefore believed that the obstruction to the peripheral blood flow in the damaged glomeruli is the causative factor. This would explain why the lesions are confined to the kidney in this disease and are, for the most part, absent in other organs. We fully agree with this explanation of the mechanism, but one must not forget that the changes in the arterioles are not unlike those that occur in any chronically inflamed tissue. Some of the changes in the vessels may be of this nature.

From morphologic studies of chronic diffuse nephritis, we have gained the impression that the vascular changes that occur in the advanced stages of this condition are often as extensive as in primary vascular disease and therefore cannot help but play a similar important rôle in the fibrosis and contraction of the kidney. If this conception is true, it may help to explain why the clinical pictures in the advanced stages of both arteriolar nephrosclerosis (primary contracted kidney) and chronic diffuse nephritis (secondary contracted kidney) often cannot be differentiated.

The kidneys in chronic diffuse nephritis differ in one important essential from those in primary arteriolar sclerosis. The former, unlike the latter, have, between the areas of ischemic sclerosis and atrophy, anatomically altered and functionally inferior parenchyma. As a result, they are rarely able to reach the extreme reduction in size of the kidneys in primary arteriolar sclerosis before azotemia and death terminate the process.

Until recently, these observations and conclusions were based only on impressions gained from microscopic studies. In order that the vascular disease in the secondary contracted kidney might be visualized more accurately, a method of injections to render the arterial circulation visible in all its ramifications was employed, which had been devised by Gross.<sup>7</sup>

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3 Volhard, in Mohr and Staehelin. *Handbuch der inneren Medizin*, Berlin, Julius Springer, 1918, vol. 3, p. 1519.

4 Fahr (footnote 1, second reference, p. 1405).

5 Branch and Linder. The Association of Generalized Arteriolar Sclerosis with High Blood Pressure and Cardiac Hypertrophy in Chronic Nephritis, *J. Clin. Investigation* **3**: 299, 1926.

6 Fishberg, A. M. The Arteriolar Lesions of Glomerulonephritis, *Arch. Int. Med.* **40**: 80 (July) 1927.

7 Gross. Studies on the Circulation of the Kidney, *J. M. Research* **36**: 327, 1917, *ibid.* **38**: 379, 1918-1919.

Bright<sup>8</sup> himself was the first to attempt a study of the circulation of the kidney in the disease that he described. The original publication contains his drawing of a kidney into which he had injected a colored solution. In response to a suggestion of Bence-Jones, Dickenson,<sup>9</sup> in 1860, perfused contracted kidneys and concluded that the increased resistance of the diseased organ to perfusion was not due to any change in the caliber of the renal artery or vein but to alterations in the more minute anatomy of the organ. In 1877, Thoma<sup>10</sup> came to similar conclusions. In 1925, Rigo,<sup>11</sup> repeating the experiments of Dickenson and Thoma, observed the same increased resistance to perfusion in both primary and secondary contracted kidneys. Within the past year, Doenecke and Rothschild<sup>12</sup> reported an increased resistance to perfusion in all types of contracted kidney associated with arterial hypertension, but failed to find any variation from the normal on perfusing the kidney in a case of subacute glomerulonephritis.

In 1916, Ghoreyeb,<sup>13</sup> using Wood's metal, made casts of the arterial bed of normal and diseased kidneys. The following year, Gross devised a more accurate method of injection, using a suspension of barium sulphate and gelatin in order to reach the glomeruli. Following the injection of this suspension, the organs were fixed, dehydrated and cleared and were also studied by means of stereoscopic roentgenograms. The architecture of the entire arterial tree, down to its minutest ramifications, was thereby visualized, both in normal organs and in contracted kidneys.

In normal organs, Gross observed a treelike arrangement with innumerable fine branches, the interlobular vessels, running a straight course perpendicular to the capsule and forming a broad even cortex. The normal architecture was that of a "spreading chestnut tree." As characteristic of the contracted kidney, he described, among other things, the marked diminution in the vasculature, the arterial tree being "withered and bare."

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8 Bright. Reports of Medical Cases, London, Longmans, Green & Company, 1827, vol 1.

9 Dickenson. On Diseases of the Kidney Accompanied by Albuminuria, *Med-Chir Tr* **43** 225, 1860.

10 Thoma. Zur Kenntniss der Circulationstoerung in der Nieren bei chronischer interstitieller Nephritis, *Virchows Arch f path Anat* **71** 42, 1877.

11 Rigo. Untersuchungen ueber der postmortale Durchstroemungskapazitaet des Nierenblutgefasssystems, *Frankfurt Ztschr f Path* **31** 1, 1925.

12 Doenecke and Rothschild. Ueber das Verhalten der postmortalen Durchstroemungskapazitaet der Blutgefasssystems der Niere bei Erkrankungen mit und ohne Blutdrucksteigerung, *Zentralbl f inn Med* **48** 866, 1927.

13 Ghoreyeb. Studies on the Circulation. 1 The Effect of Disease on the Renal Arterial Bed, *J M Research* **35** 87, 1916-1917.

Graham<sup>14</sup> recently employed a suspension of bismuth oxychloride in 10 per cent acacia and confirmed the changes that Gross described as occurring in the architecture of the arterial bed in the kidney in primary vascular disease. Graham's injection fluid was of such a consistency that it penetrated the glomeruli and also made it impossible to split the kidney before making the roentgenogram. The picture was therefore so dense that finer details were obscured. He injected the fluid into only one kidney in chronic diffuse nephritis and failed to find



Fig 1—Normal kidney into which has been injected a mixture of barium sulphate and gelatin, according to the method of Gross. The numerous parallel arterioles in the cortex form a dense broad fringe.

any deviation from the normal vascular architecture. In view of the striking alterations that we have regularly observed in this disease, we are inclined to believe that the organ that he studied was not an advanced contracted kidney but was the seat of a subacute glomerulonephritis of relatively recent origin.

<sup>14</sup> Graham. A Study of the Circulation in the Normal and the Pathologic Kidney, *Am J Path* 4 17, 1928.

## EXPERIMENTAL OBSERVATIONS

Gross did not attempt to differentiate the various types of contracted kidneys into which he injected the suspension of barium sulphate and gelatin. It was therefore important to ascertain whether the remarkable diminution in vascularity in chronic "indurative" nephritis, described by him as giving the arterial tree a "withered and bare" appearance, was characteristic only of primary vascular disease of the kidney (primary contracted kidney) or whether it also occurred and reached the same degree of development in chronic diffuse nephritis.

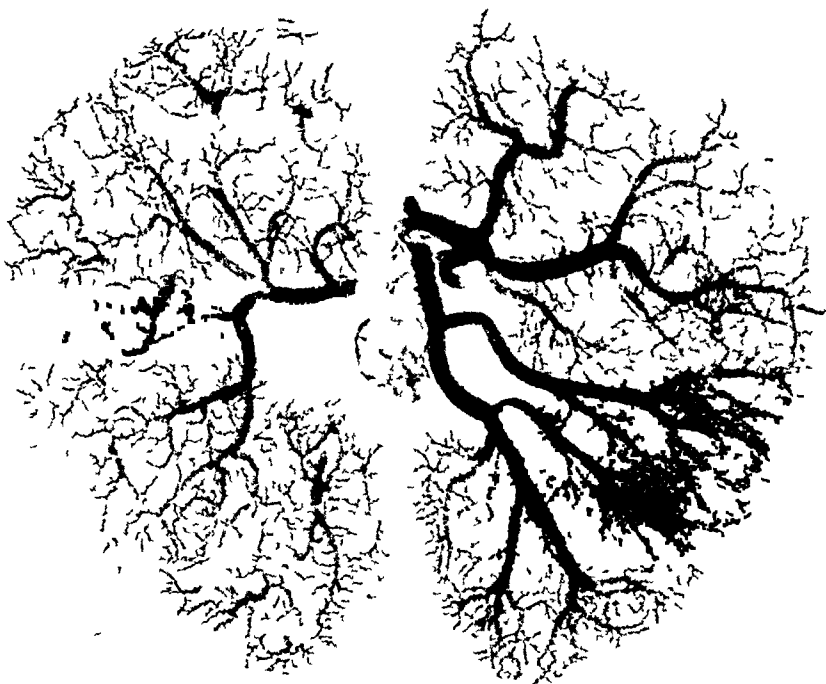


Fig 2—The kidney in arteriolar nephrosclerosis (early stage of primary contracted kidney). A marked reduction in the number of arterioles may be noted. The cortex is narrowed, and the arterioles in places run a more irregular and tortuous course.

*Primary Arteriolar Nephrosclerosis (Primary Contracted Kidney)*—Kidneys were obtained post mortem from three persons who had had uncomplicated cases of primary arteriolar nephrosclerosis. The barium sulphate and gelatin mixture was injected into the kidneys and the arterial tree studied in stereoscopic roentgenograms, and in the fixed specimens after they were cleared in methyl salicylate. A conspicuous diminution in the number of the finer branches of the arterial tree was observed, which approximated the withered and bare appearance described by Gross.

*Primary Arteriolar Nephrosclerosis Complicated by a Necrotizing Arteritis and Arteriolitis (Malignant Sclerosis of Fahr)*—The kidneys from five persons who

had had typical cases of this disease, thus complicated, were studied following the injection of the mixture of barium sulphate and gelatin. The pathologic diagnosis was based on the criteria emphasized by Fahr.

Like the ordinary primary contracted kidney, these kidneys were much reduced in size, generally to half the normal size and weight. The surface was finely granular and the cortex markedly narrowed. On the other hand, the organs were extremely red, and both the surface and the cortex were conspicuously studded with hemorrhagic dots the size of a millet seed, decidedly larger than the hemorrhagic points seen in the so-called flea-bitten kidney of acute glomerulonephritis.

Microscopically, the differentiation was easily made. Throughout the organs, areas of parenchymal atrophy and fibrosis were seen, which had been caused by



Fig 3—The kidney in arteriolar nephrosclerosis complicated by arteriolar necroses (malignant sclerosis of Fahr). Owing to closure of most of the arterioles in the cortex, the arterial system, on injection of a suspension of barium sulphate and gelatin, presents the appearance of a dead tree bereft of most of its finer branches.

arteriolar sclerosis. But, in addition, many arterioles and even arteries of medium size showed distinct necroses or inflammatory lesions of the walls. The intima in these sites was often greatly thickened, and the lining endothelium actively proliferating, so that the lumen of many of the small arteries and arterioles was being occluded. The necrotic lesions in the walls of the arteries and the proliferative changes in the lining endothelium and the intima were quite foreign to ordinary arteriolar sclerosis.

Also, numerous glomeruli supplied by these vessels showed necrotic lesions of many loops. Here and there, a necrotic loop had ruptured, resulting in a hemor-

rhage that filled Bowman's capsules and sometimes broke through and infiltrated the surrounding interstitial tissue. The capsular hemorrhages were generally larger than in ordinary glomerulonephritis, perhaps because of the high blood pressure in this condition.

Aside from the fact that the glomerular hemorrhages were more extensive than in ordinary glomerulonephritis, there were other alterations in the glomeruli that served to differentiate it from this condition. 1 Many glomeruli were not involved in the process, they appeared to be normal and their capillaries were filled with blood. 2 Many of the affected glomerular loops were not bloodless, as in acute



Fig 4—Kidney from another case showing the “dead tree” vasculature which is due to closure of the arterioles of the cortex by arteriolar nephrosclerosis complicated by arteriolar necroses (malignant sclerosis of Fahr)

glomerulonephritis. In fact, some of the damaged loops were full of blood. 3 The necrotic glomerular loops showed a peculiar hyaline droplet degeneration, which is not ordinarily seen in glomerulonephritis. Similar collections of hyaline droplets were also seen in the necrosing lesions of arterioles and arteries. 4 Although the endothelium of Bowman's capsule over the damaged loops was often swollen and desquamated, it rapidly succumbed to the necrosis. There was little tendency to form the crescents of proliferating epithelium often seen in glomerulonephritis.

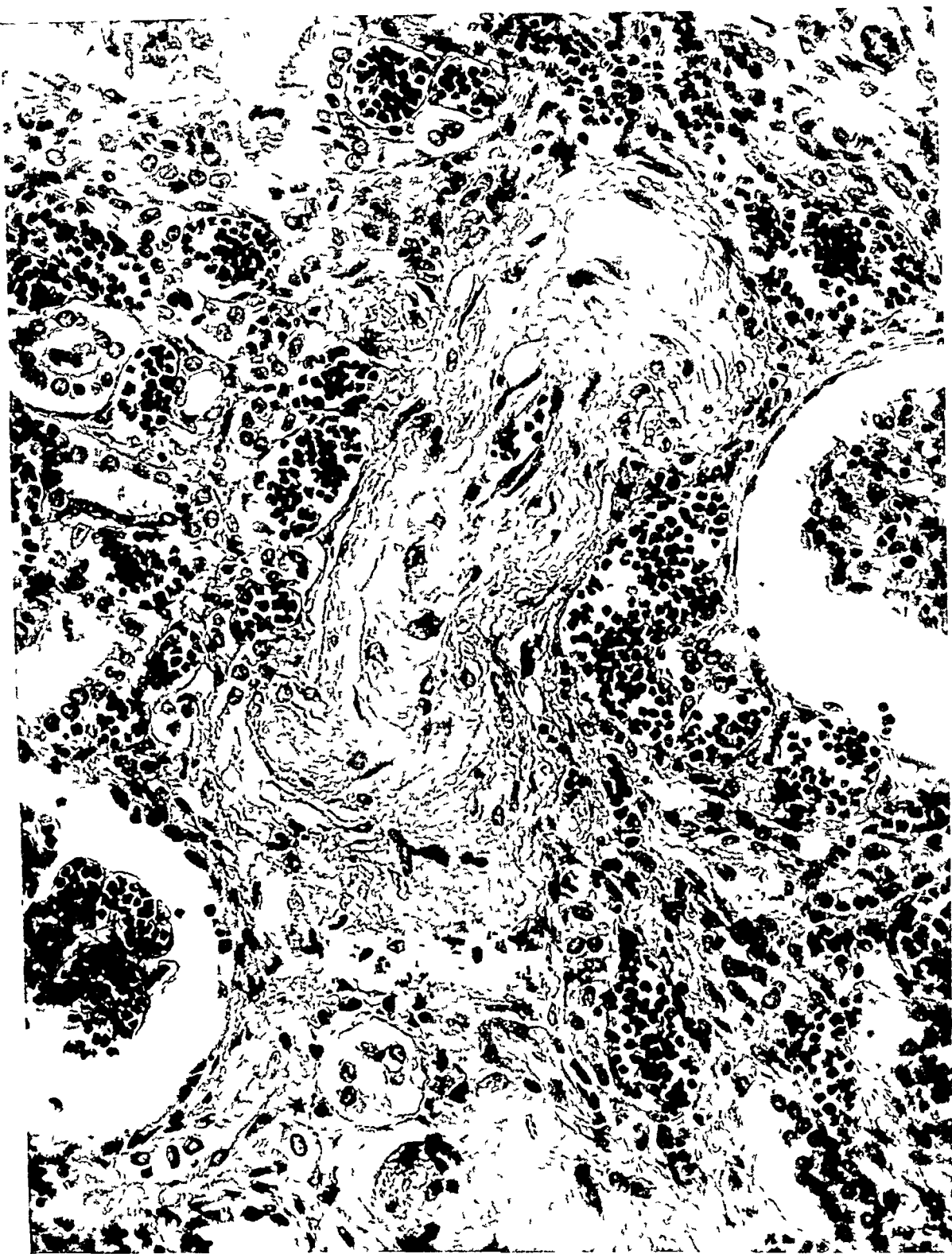


Fig 5—Arteriolar necrosis as seen in a microscopic section from the kidney shown in figure 3. Similar examples of a necrosing arteritis and arteriolitis occur throughout the organ. This photomicrograph illustrates the characteristic necrosis of the walls of the vessels and the rapid closing off of the lumen by a proliferative process in the intima.

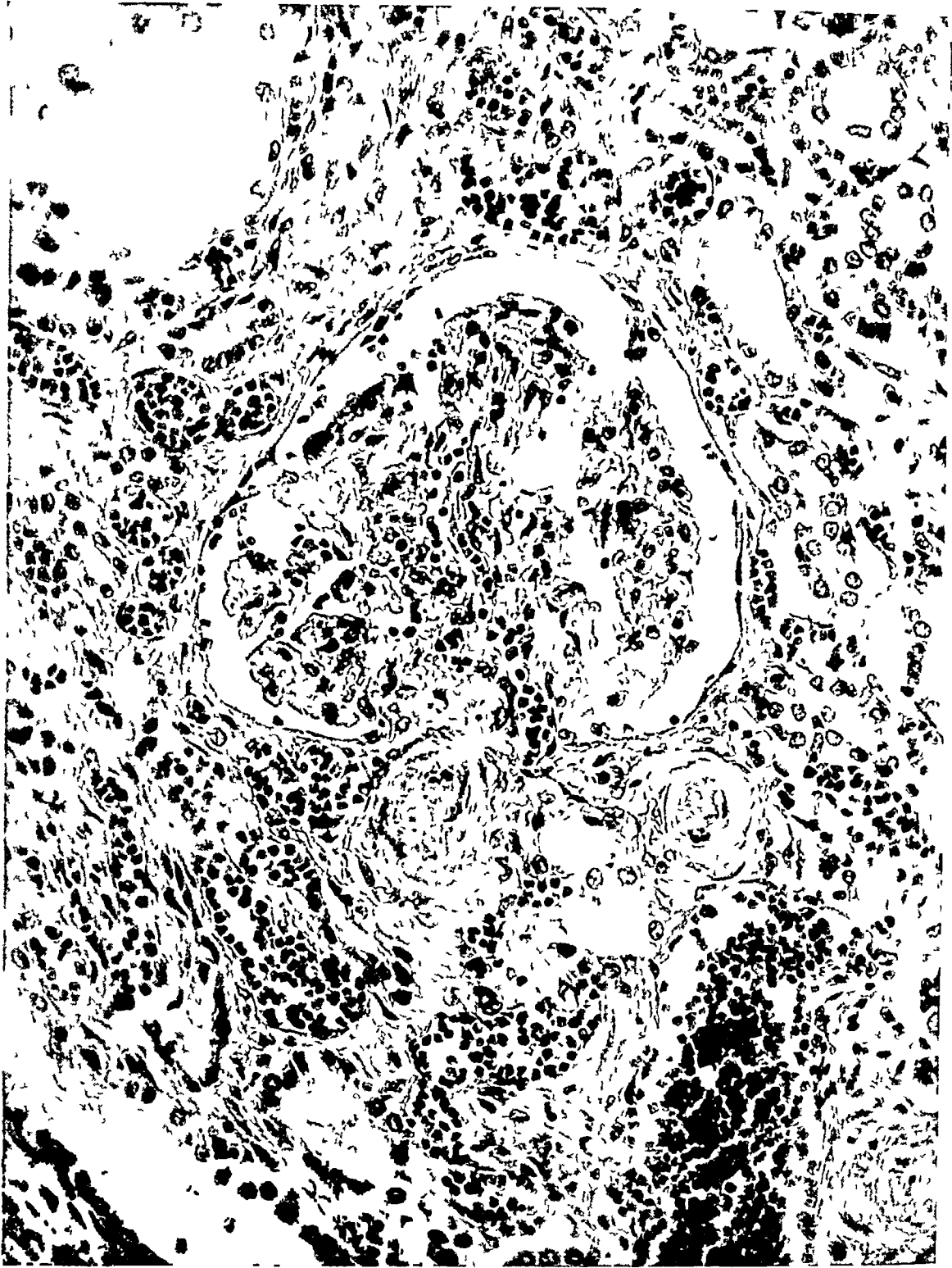


Fig 6—Arteriolar necrosis, with the characteristic necrosis of the walls of a vas afferens and the closing off of the lumen. The glomerular loops show a beginning necrosis and hyaline droplet degeneration. Some of the glomeruli in this kidney present a normal appearance, and many loops of affected glomeruli appear to be normal and contain blood.



The rapid closure of vessels resulted in atrophy or degeneration of areas of renal parenchyma and a tendency to round cell infiltration in the interstices

There can be little doubt that these five cases constituted typical examples of the condition described by Fahr as malignant sclerosis. In kidneys that were already the seat of a slowly progressive arteriolar sclerosis associated with long standing arterial hypertension, there was superimposed a complicating necrosing arteritis with rapid closure of many of the smaller arteries and destruction of many glomeruli. Death occurred in dry uremia.

The kidneys into which the suspension of barium sulphate and gelatin had been injected showed an exaggeration of the changes described by Gross. The reduction

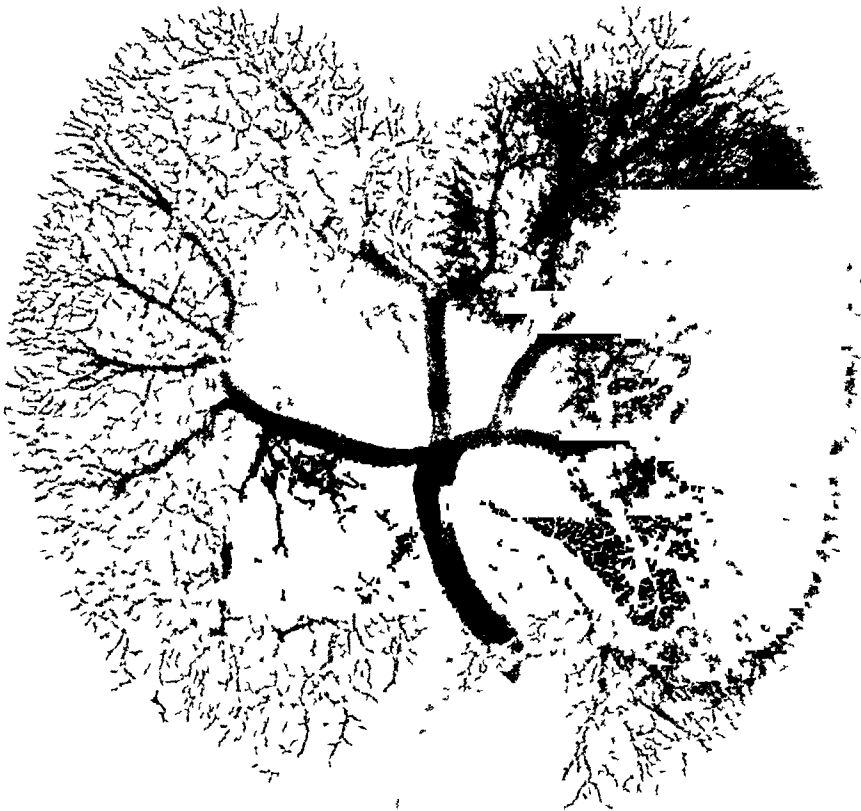


Fig 7—The kidney in subacute glomerulonephritis. Although the organ is swollen and edematous, there is not yet any conspicuous alteration in vascularity.

in the vascularity and the barren appearance of the vascular tree were marked. In fact, the vascular architecture in two cases was more like that of a dead tree, bare of most of its smaller branches.

*Acute and Subacute Glomerulonephritis*—The kidneys in four cases of early diffuse glomerulonephritis were studied. Two of the patients had died in the acute stage of the disease within a month after the onset. They showed grossly the flea-bitten type of kidney. The kidneys from both patients presented, microscopically, a most severe diffuse glomerular disease. In one of these patients, complete anuresis had been present during the last fifteen days of life.

The other two patients had died approximately four and seven months, respectively, after the acute onset. The terminal clinical pictures had been characterized

essentially by the presence of nephritic edema, azotemia and arterial hypertension. The kidneys were distinctly swollen, the parenchyma gray brown and cloudy, and in one the surface still showed minute red points of occasional hemorrhagic glomeruli. Otherwise, the gross picture was that of the large white kidney. Microscopically, the disease was diffuse, all the glomeruli being more or less involved. Many contained typical crescent formations in Bowman's capsule. The epithelium in many of the primary tubules showed marked cloudy swelling.

A study of the kidneys by the injection method in all four early cases failed to reveal any gross alterations in the arterial tree. In the stereoscopic roentgenograms

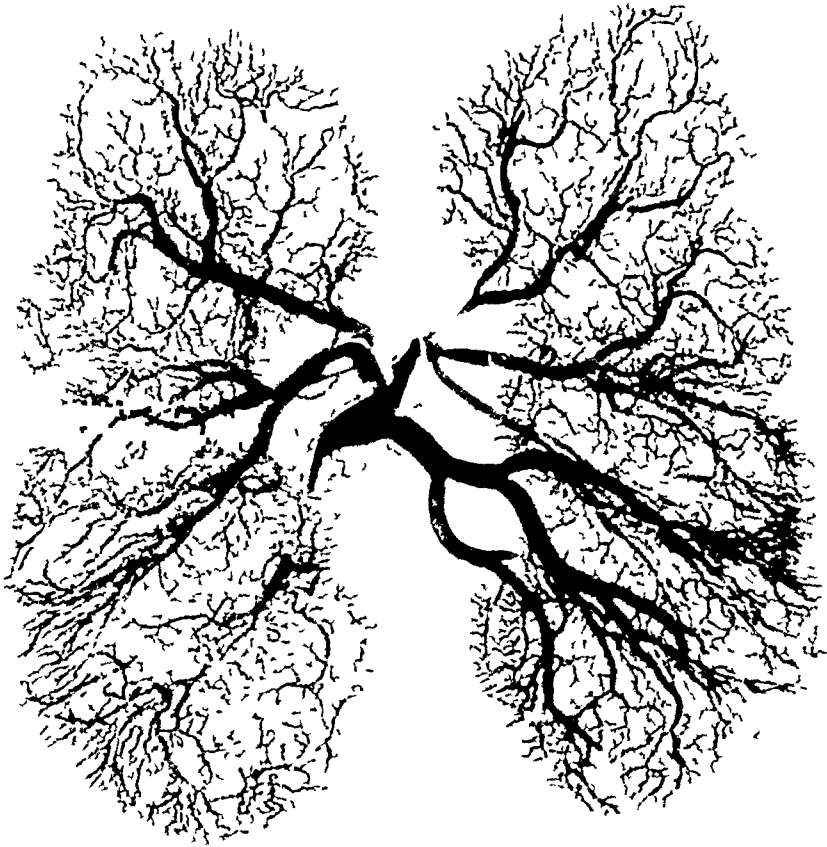


Fig 8—The kidney in chronic diffuse nephritis (secondary contracted kidney). A marked reduction in vascularity is shown. The cortex is narrow. The arterioles, which are much reduced in number, run a short and irregular course.

and in the cleared specimens, a reduction in the number of the finer interlobular arteries was not discernible. The arterial tree presented a complexity of architecture which could not be distinguished from that of the normal kidney. These early cases of glomerulonephritis served, therefore, as additional controls for the observations made in the later stages of this disease, the late secondary contracted kidney.

*Chronic Diffuse Nephritis (Secondary Contracted Kidney)*—Nine typical examples of secondary contracted kidney were studied by the injection method. Without attempting detailed description of the previous clinical course in each case

it should be mentioned that in six of the series there had been a history either of a characteristic acute glomerulonephritis in early life or of a typical nephritic edema from which there had been apparently a recovery. In three of the cases, a history of a previous acute disease was not obtainable, nor had there ever been any symptoms suggestive of nephritis until the final illness. In all nine cases, the salient symptoms were those associated with the azotemia and the arterial hypertension. In only three of the cases was any terminal edema present, and in two of these it was insignificant. Essentially, the clinical picture of arterial hypertension and dry uremia could not be distinguished from that of the primary contracted kidney.

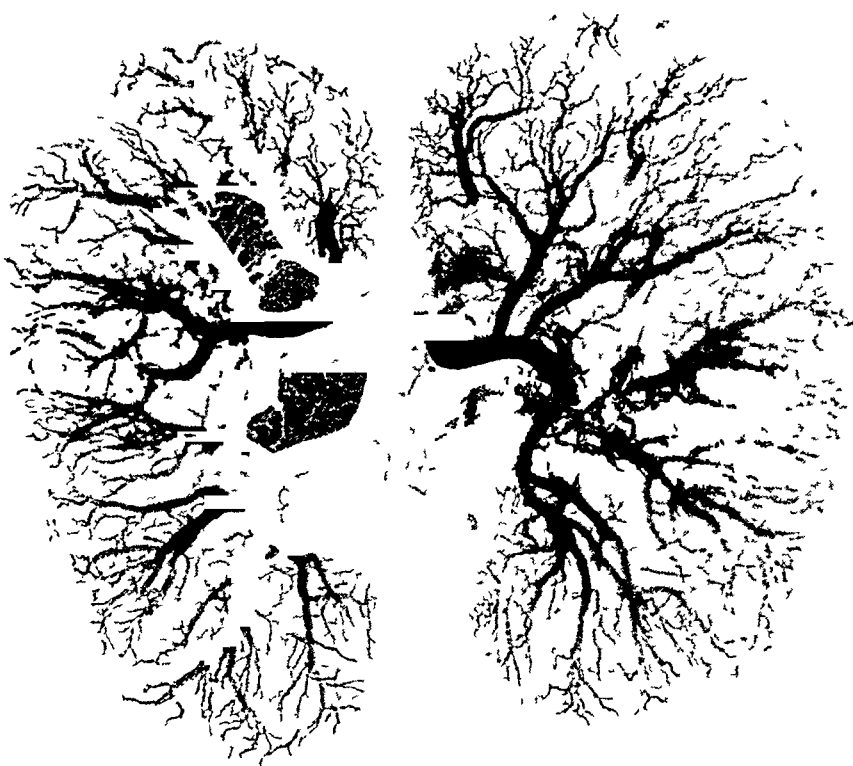


Fig 9—The kidney in chronic diffuse nephritis (secondary contracted kidney). As in figure 8, a coincidental reduction in vascularity and narrowing of the cortex are shown. In both instances, the original glomerulonephritis has long since run its course, and the pathologic process that is now responsible for arterial hypertension, renal insufficiency and death is identical with that of the primary contracted kidney.

The gross appearance of the kidneys was characteristic of secondary contraction—the moderate reduction to two thirds or one half the normal size and weight, the granular appearance of the surface, slightly coarser than that of the primary contracted kidney, and, in some, the occasional small islands of lighter colored parenchyma, which protruded on the surface and were evidences of a tendency to compensatory glandular hyperplasia or hypertrophy.

The chief microscopic criterion was the diffuse disease of the glomeruli, evidences of an old diffuse glomerular damage, as described by Loehlein<sup>1</sup>. In not a case did the microscopic observations permit room for doubt that a primary acute glomerulonephritis had initiated the pathologic process. The characteristic picture of diffuse disease of the parenchyma and sclerosis of arterioles resulting in areas of ischemic atrophy and fibrosis has already been described.

The arterial tree in all nine examples of advanced chronic diffuse nephritis, when the suspension of barium sulphate and gelatin had been injected, showed a most marked reduction in vasculature, approximately equal to that observed in advanced primary contracted kidneys. Without exception, the picture was that of the typical barren tree, and it was due to the obliteration of large numbers of arterioles and interlobular arteries.

Appreciable alterations in the vascular tree are not seen in the acute and subacute stages of glomerulo-nephritis, and therefore we do not believe that an acute damage to the arteries at the onset of the original disease can alone be responsible for the later changes. It cannot be denied that the diffuse glomerulotubular disease plays a part in the subsequent contraction of the kidney. But during the years that supervene after recovery from the diffuse nephritis, often several decades, a sclerosis of arterioles and a progressive and profound reduction in the vasculature of the kidney gradually take place, which eventually reach a point comparable to the condition of an advanced primary contracted kidney. As in the primary vascular disease, this similar reduction in vasculature due to the obliteration of many small vessels must produce atrophy of areas of renal parenchyma, replacement fibrosis and, finally, contraction of the organ.

#### CLINICAL-PATHOLOGIC CORRELATION

After recovery from acute glomerulonephritis, the glomerular capillaries that have not been completely destroyed are more or less permanently damaged, their walls remain thickened, hyaline and inelastic. Perhaps in part, because of this, the susceptibility of the tubular epithelium to toxic degenerative influences often seems to be greatly increased. The degree of glomerulotubular damage under these circulatory and toxic influences and its persistence probably determine the intensity of the albuminuria and, therefore, the occurrence of nephrotic edema.

Some cases of glomerulonephritis never pass through a nephrotic stage. Only a long latent symptomless period supervenes after recovery from the acute disease. During the latent period, which may last for several decades, the blood pressure may be normal and the urine may, at times, be entirely free of albumin.

Both types of cases, those that have and those that have not passed through a nephrotic stage, are represented in our series. In all, in the

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<sup>1</sup> Loehlein. Ueber Schrumpfnieren, Beitr. z. path. Anat. u. z. allg. Path. 63: 570, 1916-1917.

course of time, arteriole disease developed, as widespread and as significant as in the primary contracted kidney. Concomitant with the appearance of these extensive sclerotic changes in the renal vascular bed, the blood pressure became conspicuously elevated. It is at present futile to speculate on the primary importance of arteriolar sclerosis in the causation of the arterial hypertension. Certainly the persistently high blood pressure may also conversely increase the tendency to arteriolar sclerosis and arteriosclerosis.

In this stage of chronic diffuse nephritis, the pathologic process is essentially identical with that of the primary contracted kidney—the gradual reduction in finer vasculature resulting in a progressive shrinkage of the kidneys. It is therefore not surprising that, if symptoms of the original diffuse nephritis have vanished, the clinical picture in both types of contracted kidney should be indistinguishable.

This fact has been the source of much confusion among clinicians. The clinical picture of arterial hypertension terminating in dry uremia is generally associated with the primary contracted kidney. It is indeed disturbing to the clinician to be told by the pathologist that the primary pathologic process was a glomerulonephritis and that the postmortem examination reveals an advanced stage of chronic diffuse nephritis. This apparent inconsistency is largely responsible for the statement heard from some clinicians that it is impossible to correlate the various clinical pictures of nephritis with the pathologic types observed at the post-mortem table. The observations that we have just reported remove one of the chief misconceptions in this regard. Pathologists have failed to visualize the pathologic process accurately. At this late contracted state of chronic diffuse nephritis, the primary glomerulotubular damage has spent itself, and the essential pathologic process, and hence the clinical picture, is now identical with that of primary vascular disease.

#### CONCLUSIONS

The reduction in renal vasculature in chronic "indurative" nephritis described by Gross is characteristic of both primary and secondary contracted kidneys.

In primary contracted kidney complicated by a necrosing arteritis and arteriolitis (the so-called malignant sclerosis of Fahr), the "barren and bare" appearance of the arterial tree is more pronounced, like a dead tree bereft of most of its finer branches.

Similar vascular alterations, as marked as those of primary arteriolar disease, develop in patients with chronic diffuse nephritis (secondary contracted kidney) who have survived the primary glomerulonephritis for a long enough period.

It has been universally believed that in chronic diffuse nephritis the diffuse parenchymal disease is alone responsible for the subsequent con-

traction of the organ. Our studies indicate that secondary arteriolar sclerosis plays a more important rôle in the production of the secondary contracted kidney.

The clinical picture of arterial hypertension terminating finally in dry uremia is generally considered characteristic of the advanced primary contracted kidney. In our experience, the secondary contracted kidney is much more commonly found at autopsy as the cause of this picture.

Studies based on arterial injection demonstrated that the terminal stages of the processes in both primary contracted kidney and secondary contracted kidney are pathogenetically identical—a progressive reduction in the finer vascularity of the organ resulting in a steady reduction in the amount of cortical tissue. It is, therefore, not surprising that these two types of renal disease, totally different at the time of their origin, should so often give rise, in their terminal stages, to identical clinical manifestations.

# THE EXCRETION OF METHYLENE BLUE (METHYLTHIONINE CHLORIDE, USP) BY THE BILIARY SYSTEM OF THE RABBIT

ITS SIGNIFICANCE FOR THE CONCEPTION OF HEPATOGENOUS STASIS IN THE GALLBLADDER <sup>†</sup>

BÉLA HALPERT, M D

AND

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There is considerable difference of opinion concerning the purpose and functions of the biliary vesicle. According to the most widely accepted view, the gallbladder is a reservoir with the function of supplying concentrated bile whenever there is call for such in the intestine. According to another view, of more recent conception, the bile enters the gallbladder not to be stored there and expelled in time, but to be resorbed in toto by the mucosa of the gallbladder. Thus it performs at least two main functions: first of returning important bile constituents into the circulation and second by the resorption of bile, relieving and regulating the pressure within the biliary system while the sphincter of the ductus choledochus is closed.

In other words, according to this hypothesis, bile which once has entered the gallbladder does not leave it again through the cystic duct under ordinary conditions, but is resorbed by the mucous membrane of the biliary vesicle, and the constituents then returned by the way of the veins and lymphatics into the liver and into the general circulation, respectively. The arguments for and against such a conception have recently been summarized by Kasper Blond<sup>1</sup>. The fact that bile may and does leave the gallbladder occasionally in small quantities does not invalidate the conception. Our experiments with methylene blue (methylthionine chloride, USP) on the rabbit<sup>2</sup> furnish substantial evidence, if not experimental proof, that at least in this animal, when bile leaves the gallbladder through the cystic duct, this is rather an exception than the rule.

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<sup>†</sup> Submitted for publication, Nov 28, 1928

<sup>\*</sup> From the Department of Pathology and the Otho S. A. Sprague Memorial Institute, University of Chicago

<sup>†</sup> Read at the Chicago Pathological Society, Nov 12, 1928

1 Blond, Kasper. Eine neue Arbeitshypothese zur Klärung der Gallenwegsprobleme. *Arch f klin Chir* **149** 662 1928

2 Halpert, Bela, Rosi, A. L., and Hanke, Milton Theodore. Some Observations on the Function of the Gall-Bladder. Experiments with Methylene Blue on Rabbits. *Anat Record* **38** 13, 1928

It is not our purpose to present at this occasion all the data we have obtained on the excretion of methylene blue by the biliary system of the rabbit. We are more concerned at present with the data which illustrate the possibility of a hepatogenous stasis in the gallbladder, since this in turn, we believe, throws some light on the mechanism of the formation of biliary concretions.

Methylene blue injected intravenously or given by stomach tube appears in the bile, in which it can be determined by a quantitative method devised by one of us (M. T. H.). A brief description of this method and the results of some preliminary experiments with methylene blue on the rabbit have been published in the issue of the *Anatomical Record*<sup>2</sup> which contains the abstracts of papers presented at the meeting last April of the American Association of Anatomists.

In all of our experiments methylene blue was administered to rabbits in doses of 20 mg. per kilogram of body weight, that is, 2 cc. of a 1 per cent solution, in one series intravenously, in another by stomach tube.

It was found that methylene blue injected intravenously appeared in the bile in from three to fifteen minutes and reached a highest concentration—from 1:1,100 to 1:3,300—before the end of the second hour. Then, dropping gradually it showed from a fifth to a fifteenth of the highest concentration by the end of the sixth hour, the values ranging between 1:9,000 and 1:36,000. The bile removed from the gallbladder at the same time, i. e., six hours after the injection, usually contained from two to twenty-two times as much methylene blue as that contained in the last specimen of bile obtained from the ductus choledochus. Not only that, but at times the concentration of methylene blue in the bile removed from the gallbladder was much higher (1:720, 1:800) than the highest concentration ever reached in the bile collected from the ductus choledochus. The curve indicating the methylene blue content of the bile coming from the liver was a regular one—a sharp rise to the peak of a highest concentration was followed by a gradual decline. On the other hand, during the whole period of this decline and up to the end of the experiment, the methylene blue content of the bile in the gallbladder increased and at the end of the experiment was usually found to be many times higher than that coming from the liver. Had there been an occasional admixture of the bile from the gallbladder, with its high content of methylene blue to that coming from the liver, the curve of declining methylene blue concentration in the ductus choledochus would have exhibited irregularities. As the curve showing the methylene blue content of the bile collected from the cannulated ductus choledochus remained regular, however, it may be assumed that no bile left the gallbladder.



In the feeding experiments the amount of methylene blue given by stomach tube was exactly the same as in the experiments with injections

Bile collected from the cannulated ductus choledochus twelve, eighteen, twenty-four, thirty and thirty-six hours after the administration of methylene blue by stomach tube contained little if any methylene blue. On the other hand, bile removed from the gallbladder at the same time invariably contained the dye. Bile collected from the cannulated ductus choledochus forty-two, forty-eight, sixty and seventy-two hours after the administration of methylene blue by stomach tube did not contain methylene blue. On the other hand, bile removed from the gallbladder contained the dye even after seventy-two hours in most instances.

When we examined the data on the feeding experiments more closely we noted that in none of the thirty-four animals which were opened between the twelfth and the thirty-sixth hours after feeding of the dye did the bile collected from the ductus choledochus contain methylene blue in a higher concentration than 1:23,000, as a matter of fact, in fourteen the bile did not contain any methylene blue. Yet the bile in the gallbladder of all of these animals contained the dye in concentrations between 1:1,200 and 1:10,000 in nineteen, and between 1:10,000 and 1:25,000 in eleven. The results in the forty-two, forty-eight, sixty and seventy-two hour groups of thirty-two animals are uniform. As mentioned before, in none of the animals did the bile collected from the cannulated ductus choledochus contain any methylene blue. Yet the bile in the gallbladder at this time contained the dye in more than half of the specimens, in concentrations ranging between 1:4,850 and 1:26,000.

In addition to all that has been said, attention should be called to the fact that the amount of bile delivered through the cannulated ductus choledochus during an experimental period of six hours averages about 10 cc per hour, that is, the liver of a rabbit weighing 3 Kg produces, conservatively estimated, 240 cc of bile per day, and that the average capacity of the gallbladder of the rabbit is about 3 cc. Furthermore, in the feeding experiments the animals were kept on their usual diet, and there was always food in their cages. Under these conditions it is hard to conceive how methylene blue could remain in the gallbladder of an animal for a period of at least forty-two hours during which not less than 420 cc of bile not containing the dye could have come from the liver, unless we give up the idea that the function of the gallbladder is to empty and to refill. The tenacity with which the dye is retained in the biliary vesicle long after the liver has ceased to produce bile containing the dye is surely one of the strongest arguments favoring the assumption that bile does not leave the gallbladder through the cystic duct under ordinary conditions. This circumstance of course, calls for a change in the current conception of stasis in the gallbladder.

The term "functional biliary stasis" originated with John Berg, the Scandinavian surgeon. He urged<sup>3</sup> that a strict differentiation be made between the mechanical type of biliary stasis, i. e., one due to a mechanical obstruction to the free passage of bile into the duodenum, and a "functional biliary stasis" (mainly in the gallbladder) due rather to functional disturbances than to easily demonstrable anatomic conditions. "Functional biliary stasis," however, as conceived by John Berg, is a vague term, since its causes are unknown. Functional biliary stasis, as one of us has defined it elsewhere,<sup>4</sup> is a disharmony between the bile contained in the gallbladder and the resorptive function of the mucosa of the gallbladder. This definition of functional biliary stasis assumes, of course, that the mucous membrane of the normal gallbladder is capable of resorbing all of the bile constituents and that a disturbance of this resorptive function is the factor leading to stasis of bile in the gallbladder. The site of the process leading to stasis of bile in the biliary vesicle may be, of course, in the gallbladder itself, cystogenous stasis. Or, the quantity or quality of the bile produced by the liver may be such that the mucous membrane of the normal gallbladder is unable to resorb it completely, the liver rather than the gallbladder thus being responsible for the resultant stagnation. This type of stasis may appropriately be termed, as one of us has pointed out elsewhere, hepatogenous stasis. Finally, of course, both the gallbladder and the liver may be concerned.

Our experiments with methylene blue on the rabbit thus furnish a striking example of hepatogenous stasis in the gallbladder. With the bile from the liver a substance, methylene blue, is poured into the gallbladder, the mucosa of the latter apparently cannot resorb the dye fast enough to cause its rapid disappearance, and so the dye stays there for days.

This experimental result supports the idea that something analogous happens in cases of marked cholesterolemia, when the cholesterol content of the bile is correspondingly exaggerated. Apparently due to the increased output of cholesterol by the liver, the mucosa of the gallbladder becomes, so to speak, saturated with the lipid substances which it has resorbed from the bile. In such conditions, the cholesterol content of the bile in the gallbladder becomes greater and greater, and while the other bile constituents, those holding the cholesterol in solution, are being resorbed, the concentration finally may reach a point at which the cholesterol will crystallize out at the slightest provocation.

3 Berg, John. Einleitungsvortrag zum Thema "Gallensteinleiden," Arch f Klin u 126 329, 1923

4 Halpert, Bela. Neue Wege in der Gallenblasenforschung, Med Klin 20 408 and 1830 1924

In conclusion, we may say that the significance of the data obtained from the experiments with methylene blue on rabbits is manifold

- 1 The data contribute experimental evidence that the bile does not, under ordinary conditions, leave the gallbladder through the cystic duct

- 2 They furnish a striking example of stasis in the gallbladder for which the liver is responsible (hepatogenous stasis)

- 3 In view of the possibility of creating conditions analogous to those described here for methylene blue, but with agents with more pronounced bactericidal action, they may indicate the road leading to a much desired goal, a successful chemotherapy of the gallbladder

# General Review

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## THE PATHOLOGY OF PRIMARY CARCINOMA OF THE LUNG <sup>1</sup>

CARL V WELLER, M D

ANN ARBOR

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\* From the Department of Pathology, University of Michigan

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Interest in carcinoma of the lung and bronchi is gaining momentum if one may judge by the rapidly growing literature on this subject. The nature of the disease is such as to compel the attention, and invite the contributions, of those concerned with several branches of medical science. The internist, the surgeon, the radiologist and the bronchoscopist each feels that it lies peculiarly within his field, while to the pathologist it presents certain as yet unsolved problems that prove exceedingly attractive. No other form of neoplastic disease is more intriguing from the standpoint of incidence than primary carcinoma of the lung, for within a generation it appears to have become one of the common forms of malignant disease, instead of the rarity which it was believed to be at the beginning of the present century. Is this alteration in incidence real or only apparent? If it is real, and many competent pathologists are convinced that it is, what are the factors in the life of the time which have brought about such a change that one now sometimes sees the word "epidemic" figuratively used in connection with this condition? Answers to these questions will be of importance, also, in connection with the problems of malignant disease in general.

Recent rapid advances in thoracic surgery challenge the internist and the clinical pathologist to diagnose carcinoma of the lung at a sufficiently early stage so that surgical intervention will be possible. This is rarely accomplished, although the diagnosis is being made more and more frequently on the living patient rather than at autopsy. The roentgenologist, aided by intrabronchial use of radio-opaque substances, and the bronchoscopist, supported by microscopic biopsy, are at present the chief aids in securing early diagnosis. Thus from many sides have arisen interests which have so augmented the literature of primary carcinoma of the lungs and bronchi that it is unusual to open a journal without finding some reference to this subject. Many interesting reports of cases of carcinoma of the lung are concealed under other titles. For instance, Yokohata's paper on microscopic metastases of cancer in the spleen contains descriptions of four typical cases of carcinoma of the lung. An annotated bibliography if complete would, alone, exceed the limits of this review.

## HISTORICAL NOTE

Of necessity, the early history of primary carcinoma of the lung lies in obscurity. The best historical survey is that of J. Wolff, who has reviewed rather critically some of the earlier references. Morgagni's description of a case in 1761 is sometimes quoted as the earliest gross account of primary carcinoma of the lung. It rests on slender evidence. A man, 36 years of age, who had had blood-streaked sputum, a cough and pain in the chest, died on the seventh day of the disease "in consequence of his expectoration being wholly suppressed." Bilateral pleural adhesions were found, particularly heavy over the upper right side anteriorly. Here a "cancerous ulcer lay hid in the lungs the seat, perhaps, of an inveterate disease." A polypoid mass in the right ventricle provided a possible explanation of pulmonary infarction. A second observation made on a woman 40 years of age, who had a large tumor of the heel, certainly had to do with metastatic sarcoma of the lungs. A case observed by van Swieten, in which the upper portion of the right lung of a man 50 years old was scirrhus, may well have been pulmonary carcinoma, although esophageal carcinoma could not be definitely excluded.

The term "*phthisie cancéreuse*" was used by several writers before 1810, but then descriptions left uncertainty as to the primary neoplastic nature of the conditions described. In that year Bayle, under this same name, described three cases. The first was that of a man, 55 years old, who was attacked with dyspnea and a dry cough and had a mucopurulent sputum with hemoptysis. The duration of the disease was eighteen months. A soft, fluctuating tumor finally appeared above the right clavicle. At dissection, both lungs were found to contain numerous tumors of rounded form and of a lardlike consistency. Although other primary growths were not found in the body, the description of the tumors in the lung suggests that they may have been metastases. Bayle's second case, in which numerous encephaloid tumors were found in the lungs of a man 35 years of age, who had suffered amputation of the arm for a rapidly growing tumor, was certainly an example of pulmonary metastasis. The third case was that of a man, aged 72 whose illness was thought to be of but six weeks' duration. Pain in the chest and epigastrium, cough, white opaque sputum, obstipation, enlargement of the liver and three small hard movable bodies in the epigastrium and the right hypochondrium were the symptoms. At dissection, the root of the left lung was found to be occupied by a shining, white, medullary mass. In this and in the lung itself, tuberculous areas could be distinguished from those which were cancerous. The presence of numerous large metastases in the liver rendered doubtful the primary nature of this case which might have been a bronchiogenic carcinoma so far as the description of the lung itself is concerned.

William Stokes, in 1837, stated that cancerous disease of the lung was to be encountered in two forms. In the first, a degeneration of the lung occurred so that it was transformed into a cancerous mass without any tumor being produced. In the second, the scirrhus or encephaloid matter formed a tumor which was at first external to the lung, but ultimately displaced it. He recognized the great variety of physical manifestations which an intrathoracic mass of the second type could produce through displacement of the lung, compression of the esophagus, trachea or bronchi, or the obliteration of the subclavian or carotid arteries or of the innominate vein. Later, in 1842, he collected and analyzed a group of cases of malignant disease of the lung, partly from his own experience and partly from the literature, including the important case of Graves, which was the first in which a careful physical examination was carried out. In this paper, Stokes discriminated between nine different types of thoracic cancer and noted the combination of that condition with empyema, with pulmonary gangrene, with bronchiectasis and with bronchitis. Although obviously secondary carcinoma is confused with possibly primary cancer among the cases quoted, sound clinical observations were made and important principles were formulated. These may be illustrated by quoting from a long list of conclusions:

That dysphagia, tracheal stridor, feebleness of one pulse, difference of respiratory murmur from pressure on the bronchial tube, displacement of the diaphragm and dilatation of the heart may occur.

That the following symptoms are important as indicative of this disease: pain of a continued kind, a varicose state of the veins in the neck, thorax, and abdomen, oedema of one extremity, rapid formation of external tumors of a cancerous character, expectoration similar in appearance to currant jelly, resistance of symptoms to ordinary treatment.

These early observations were followed by a constantly increasing number of reports of cases. The development of histopathology led to analyses based on the types of cells that characterize the structure of the growths and to classification according to histogenesis. Thus, near the end of the century, the important studies of Kurt Wolf and of Passler collected the available cases. Reinhard had found twenty-five cases in 1878 while Wolf listed thirty-one in 1895. Not all of these were microscopically verified. In 1891, Werner could find but nine fully verified cases, but in 1896 Passler listed seventy which he believed to be authentic. Adler's monographic work published in 1911 was based on 374 cases of carcinoma of the lung and 80 cases of sarcoma, but here, again, some cases were admitted without microscopic verification and others in regard to the primary nature of which serious doubt must be entertained.

In more recent years, the great apparent increase in the number of cases of primary carcinoma of the lung has stimulated statistical study and speculation as to the etiologic factors. The tumors of the lungs of the Schneeberg miners have been reconsidered. Much attention has been given to the possible effect of pandemic influenza as a cause of increased incidence. The past ten years have been characterized by a realization of the great frequency of primary carcinoma of the lung and of the importance of this localization in connection with the whole problem of cancer.

#### INCIDENCE

*Inherent Weakness of Most Statistical Studies*—As is true of all cancer statistics, those dealing with primary carcinoma of the lungs and bronchi are of value only to the extent that the material units have been critically selected. The authenticity of the individual case is the crucial test. Obviously, only those reputed examples of primary carcinoma of the lung are of value on which a complete autopsy has been done. Certainly, too, there must be microscopic verification of each case, if results are to be fully accepted. Routine microscopic examination reveals many errors in the conclusions of even the most experienced gross pathologists. Doubtful cases should be excluded from collected series. For instance, a patient with massive infiltration of the mediastinum and root of a lung and a small hard nodule of the same type of carcinoma in the thyroid is more apt to have a primary carcinoma of the thyroid than a primary bronchiogenic carcinoma. Also, those examples in which multiple separate masses of carcinoma are found in both lungs and primary carcinoma is not observed elsewhere, are best interpreted as instances of hidden primaries. Every experienced prosecutor can recall autopsies in which painstaking search failed to disclose a primary site of malignant growth although abundant secondaries were present in the lungs or the liver. The microscope might have shown in such cadavers a small area of long standing malignancy in the prostate, breast, thyroid or elsewhere. Cases are encountered, too, in regard to which positive conclusions cannot be drawn even with thorough microscopic study. In the desire to have extensive series of cases to report these and other errors have been allowed to become both frequent and obvious in many of the collected series. In studies which are only statistical, the reader is at a loss to know how critical the compiler may have been in selecting his original units. There is still need for statistical studies based on carefully selected and fully authenticated cases of carcinoma of the lung.

*Spontaneous Occurrence in Animals*—Primary neoplasms of the lungs and bronchi have been numerous reported as discovered in the lower animals, in a wide range of genera. Many of these tumors were



not well studied, so that there is doubt as to the primary cancerous nature of some which have been so classified. Those interested in the wide occurrence of neoplasms of the lung in general will find much of interest in the compilations of Fox and Sticker. Fox found only 4 primary tumors of the lung among 34 neoplasms discovered in 2,533 wild animals dying in captivity on which he made autopsies. These occurred in the musky, porcupine, Malayan civet and rabbit-eared bandicoot. Sticker found 30 cases of primary cancer of the lung among 1,026 instances of primary cancer of all organs occurring in domestic animals.

Fuchs, in 1886, described what he believed to be a primary bronchial carcinoma of the cat. Both lungs were involved in a nodular manner, the microscopic picture was that of a mucin-producing, cylindric-cell adenocarcinoma and there were metastases to the bronchial and axillary nodes. Diffusely infiltrating carcinoma of the lung of the cat was described also by Kitt, and Sticker found the lung to be the site of 3 of the 21 instances of primary carcinoma that he listed for this animal.

In the dog, Sticker found 10 malignant neoplasms of the lung in 766 autopsies. The earliest recognition of primary carcinoma of the lung in this animal appears to have been that of Johne (1880), although he did not give a detailed histologic description. A carcinoma made up of large cylindric cells in a lower lobe of a lung of a dog was reported by Seiger. Metastases were not found. A similar neoplasm was described by Lienaux, while the mucinous carcinoma of the lung reported by Rievel was thought to have had its origin from the flattened alveolar epithelium and to have undergone a secondary mucinous degeneration.

Few reports of primary carcinoma of the lung in cattle are to be found in the literature. Sticker was able to collect but three cases and these were of uncertain value.

Primary carcinoma of the lung in horses has been described several times (literature reviewed by J. Wolff). Grammlich's case showed a left bronchus broken through by the neoplasm.

Wolff was able to collect three probably primary epithelial neoplasms of the lungs of sheep. One of these, that of Ebel, is of special interest because of the diagnosis of "adenoma proliferum papillare," suggesting that it might have been similar to the neoplasms which are common in mice. It was believed, however, to have had its origin in the mucous glands of the bronchial wall. Atypical, but nonmetastasizing, epithelial proliferations, which were chiefly of alveolar origin, occurred in the lungs of sheep suffering from the South African disease called "jagziekte" (Cowdry). These were often extensive and presented a definite adenomatous appearance. An annular bronchial polyadenoma of unknown causation was described in the sheep by Ball.

In the rabbit, as in the guinea-pig, carcinoma of the lung must be rare indeed, considering the large number of these animals which are examined in various laboratories in which the presence of a neoplasm would arouse interest. Wolf<sup>1</sup> was able to collect but two examples for the rabbit. One of these was described as a "carcinoma simplex," the other as an "epithelioma." He listed a single "adenoma" as the only primary epithelial neoplasm of the lung of the guinea-pig reported up to the time of his study. Apparently the rat is also relatively free from spontaneous pulmonary carcinoma. In connection with the examination of rats for the plague at San Francisco, McCoy did not find one with tumor of the lung, although 103 with other tumors were discovered.

Primary epithelial tumors of the lungs of mice have attracted attention. The first of these was described by Livingood in 1896. A small white boss, about 5 mm in diameter, was found projecting from the surface of the lung. Microscopically, this small mass was thought to present the appearance of an adenocarcinoma, and at one point it could be seen to arise from within a bronchus, growing as a papilloma within its lumen but breaking through the wall of the bronchus and dispersing in the surrounding tissue. Haalund evidently saw the same type of growth in 1905. Tyzzer described a number of such tumors in detail in the following two years. Among about 800 mice he found 16 with spontaneous primary neoplasms and 12 of these had what might be termed "papillary cystadenomas" of the lungs. In only one instance was the tumor large enough to interfere with function. An encysted worm was present in one lung, but it was not in relationship to the tumor. All of these tumors corresponded to a single type, but with minor variations. They were all situated at the periphery of the lung and were covered externally by pleura and consisted essentially of irregular folds and processes of supporting tissue covered by epithelium. Some were more cystic, and others more compressed, than the general type. These growths seemed to be primarily independent of the bronchi, but this point could not be definitely determined in each instance. While multiple nodules were found in some cases, proof of metastases was lacking. Nevertheless, the extension of the tumor into the bronchi, in two instances, was taken to indicate the malignant character of this type of growth. Haalund subsequently examined 30 nodules in the lungs of 19 mice. Most of these were small adenomatous nodules and did not exhibit signs of active growth. Some, however, invaded the surrounding lung tissue and the lumina of the bronchi and of the blood vessels. One nodule composed of squamous cells was found. The theory was advanced that the adenomatous nodules might have developed at the sites of earlier infarcts due to nematodes. This was based on the distribution of the lesions and could not be definitely proved, but was an attractive suggestion, for such verminous

infarcts were found in corresponding areas of the lung Tyzzer added four or five examples of the epidermoid type, in a later report, which included also his earlier cases of the type of cystadenoma, making a total of 52 neoplasms of the lung in a series of 83 tumors At about the same time, Jobling studied 9 primary tumors of the lungs occurring in 8 mice All of these animals had neoplasms of other types elsewhere All of the tumors of the lung were more or less adenomatous, some being more medullary than others Some were in apparent relationship to bronchioles Metastases were not found, but there was evidence of invasive growth

In the first 6,000 mice autopsied from Miss Slye's stock (Slye, Holmes and Wells), 160 mice were found with nodules in the lungs that might fairly be classed as tumors Twenty of these were classified as highly malignant on the basis of their pronounced heteroplastic character with evidence of active infiltration and the production of secondary growths elsewhere in the lung The investigators concluded that these tumors of the lungs might have arisen from either alveolar or bronchial epithelium, and that ordinarily the origin of the growth cannot be determined from the character of the epithelium For the common papillary type, the term "papillary adenoma" was considered more appropriate than "papillary cyst-adenoma" The epidermoid type, examples of which were described by Tyzzer and Haalund, was not represented in this material Evidence was not found to support the contention that such nodules develop at the site of infarcts produced by nematodes Of importance, as conclusively demonstrating the malignant nature of certain of these growths, was the discovery of metastases outside of the lung in four instances, to the mediastinal lymph nodes, the chest wall, the diaphragm and the kidney

Growths of this type, but usually without highly malignant characteristics, are frequently encountered Those attempting the production of pulmonary neoplasms in mice by insufflation of tar and by other experimental methods must recognize the incidence of spontaneous occurrence (Block and Dreifuss) Bonne found them in both tarred and untarred animals He stressed the evidence of origin on the basis of an old pneumonia, for it appeared to him that such tumors arose in an area altered by pneumonia and that later the pneumonia completely resolved but the tumor continued to grow

Thus, a survey of the spontaneous occurrence of primary epithelial neoplasms in the lungs of lower animals shows that only in reference to mice have there been detailed studies of a considerable number of such neoplasms The typical form in this animal is entirely different from the form usual in man The one described for the sheep by Eber was probably of the same type as that found in mice It is especially striking that tumors in mice arise almost exclusively in the

periphery of the lung while in man a growth radiating from the hilum is the more common. It is also evident that a considerable number of irritative factors are concerned with the production in lower animals of atypical growths in the lungs which often have some, but not all, of the characteristics of true malignant blastomas.

*General Incidence in Man*—The only important statistical evidence in regard to the incidence of primary carcinoma in man is that based on experience in autopsies. Clinical diagnoses and mortality

TABLE 1—*The Incidence of Primary Carcinoma of the Lung*

Compiler	Period	Autopsies	Carcinomas	Carcinoma of Lung	Percent- age of Carcinoma of Lung in All Autopsies	Percent- age of Carcinoma of Lung in All Types of Carcinoma
Tanchou	Before 1844		8,289	5		0.09
Reinhard	1852-1876	8,716	345	5	0.057	0.92
Wolf	1877-1884	4,172		9	0.21	
Fuchs	1854-1885	12,307		8	0.065	
Passler	1881-1891	9,246	870	16	0.17	1.83
Wolf	1885-1894	7,228		31	0.423	
Kikuth	1889-1899	13,777		10	0.07	
Feilchenfeld	1895-1900		507	22		5.3
Redlich	1900-1905		496	31		6.3
Kikuth	1900-1911	22,819			0.39	
Bejach	1908-1913		692	33		4.8
Briese	1898-1916	12,971	1,287	60	0.47	4.51
Bliz	1910-1919			18		2.57
Barron	1899-1921	4,362		13	0.29	
Stahelin	1900-1924					4.0
	1910-1914					2.2
Berblinger	1915-1919			42		2.9
	1920-1924					8.3
Lubarsch	1920	86,216	8,301	450	0.52	5.4
Kikuth	1912-1923	21,588+		146	0.7—	
Grove and Kramer	1917-1924	3,659		21	0.57	
Breckwoldt	1914-1925				0.38	3.2
	1895-1904	10,167	763	8	0.07	1.04
Holzer	1905-1914	9,405	766	18	0.19	2.36
	1915-1924	10,190	733	48	0.47	6.69
	1900-1906					5.1
	1907-1913					6.83
Seyfarth	1911-1918			307		11.23
	1919-1923					8.75
	6 mo. of 1924					15.5
Magarinos and Penna	Before 1927	1,531	99	3	0.195	3.09
Wells	1927		403	17		4.2
Weller	1892-1927	2,450	244	10	0.4	4.1
McCrae, Funk and Jackson	1924-1927	621	53	4	0.64	7.5

returns are alike too uncertain to be worth considering. The improvement in the clinical diagnosis of neoplasms of the lung, observable in the past five years, presages a time when such diagnoses will, however, be sufficiently accurate to be of value.

Table 1 includes the more important statistical studies. The arrangement is chronologic so far as is possible. Some overlapping of the years, of course, occurs. The final year of each report determines its position in the table. Some repetitions of data also occur, for successive workers in one laboratory have each incorporated at times data previously used.

This is not the place to discuss the worth of existing statistics of cancer. So many variable factors influence the segregation of human material, as Wells has pointed out, that differences are bound to arise in statistical evidence gathered from various sources. The best evidence at our disposal, however, indicates that, at present, in Europe and in America, primary carcinoma of the lungs and bronchi is found in about 0.5 per cent of all autopsies and in about 5 per cent of all deaths from carcinoma.

*The Trend of the General Incidence*—Reference to table 1 will show that there has been a change in the apparent incidence of carcinoma of the lung. Prior to 1900, the percentage of incidence of carcinoma of the lung at autopsy ranged between 0.057 per cent (Reinhard) and 0.428 per cent (Wolf). The higher figure was not approached by any other study, yet it is below the probable percentage of incidence at the present time, while the lower figure is about one tenth of the present percentage. This trend has been recognized by practically all who have compiled statistics on this subject since 1900. There is some evidence to show that this apparent increase may have reached a fixed high level or may have fallen off slightly. The experience of the next ten years should settle this point. A summation of statistics by periods compiled by Brunn gave the following result:

From 1872 to 1898, 382,671 autopsies yielded 159 cases of primary pulmonary carcinoma, or 0.04 per cent.

From 1898 to 1916, 192,271 autopsies included 488 cases of primary pulmonary carcinoma, or 0.24 per cent.

From 1916 to 1924, 33,308 autopsies showed 71 cases of primary pulmonary carcinoma, or 0.21 per cent.

The grouping of these cases, made necessary by the use of statistics from various sources, fails to show that it was about the year 1910 that the sharpest rise in incidence occurred.

There can be no question of the apparent increase in the incidence of this condition as shown by the statistics of autopsies, but there is a serious question whether or not this represents an actual increase. Here opinions differ widely (Stahelin, Holzer, Kikuth, Berblinger, Breckwoldt, Briese, Fried and many others). Ewing thinks that the increase in attention to the disease has augmented the number of cases of it recognized. There can be no doubt that this is an important factor, especially as regards reports of isolated cases. The same factor may operate also in large autopsy services in which routine microscopic control is not carried out. The knowledge of the frequency of bronchial carcinoma may lead to that diagnosis being made when in reality the neoplasm of the lung is secondary to some hidden primary growth for which no adequate search has been made. In this connection, Stahelin pointed out that statistics of autopsies are based too often on diagnoses and not on

objective observations, and, further, that diagnoses of carcinoma of the lung made at autopsies are largely institutional diagnoses, and that a knowledge of the diagnostic value of the x-ray and the use of it causes physicians serving homes to send a larger proportion of patients with obscure conditions of the chest into hospitals than was formerly the case

The factors which have brought about the statistical increase in the incidence of carcinoma in general, such as the shifting distribution of ages in the population, also influence in the same manner the incidence of the condition under discussion. It is rather striking that the proportion of cases of carcinoma of the lung in all cases of carcinoma runs, in practically all statistics, at about ten times the proportion of cases of carcinoma of the lung found at all autopsies. Thus the increase in the number of cases of carcinoma of the lung cannot be explained by the increase in the incidence of carcinoma in general, although influenced by it.

If the increase in the number of cases of carcinoma of the lung is only apparent, what were the unrecognized cases of carcinoma of the lung called at autopsy thirty and forty years ago? Some may have been called metastatic neoplasms and others, chronic or fibrocaseous pneumonia. One can be certain that many were called sarcomas. Carcinoma of a relatively undifferentiated type of cell has often passed as small round-cell sarcoma, and areas of spindle cells are frequently seen in bronchiogenic carcinoma (Ewing). As the number of cases of carcinoma of the lung increased, the number of cases of primary sarcoma of the lung decreased, but the total number of cases of sarcoma was not great enough to explain, alone, the changing incidence.

Thus one might conclude that the increase in the number of cases of pulmonary carcinoma may be due only to an alteration in the character of our statistics (Fried). If, however, one tabulates the statistics of successive periods in the same institution and that one in which there is continuity of diagnostic standards and often even of personnel, and finds there an increase in the incidence of carcinoma of the lung, one must give the increase more serious consideration. The statistics of nine institutions are presented in this manner in table 2. I can illustrate the method by reference to the results at the University of Michigan, although I realize that here the total number of cases was so small that the effect of chance distribution could hardly be excluded. In the first 1,000 autopsies, only one case of carcinoma of the lung was found (0.1 per cent). In the second 1,000 autopsies, 5 were noted (0.5 per cent). In the first 450 cases of the third 1,000 there have been 4 examples (0.8 per cent). Every autopsy in the series was carefully controlled by complete microscopic study and the directorship of the

laboratory (held by Aldred S. Waithin) remained constant throughout the period represented. Any variable factor must have been inherent in the material itself, either through uneven segregation of the patients in the hospital or through an increase in the number of cases of carcinoma of the lung. I am sure that equally well controlled evidence is available from other institutions included or not included in table 2.

It seems impossible to reach a conclusion on this question at the present time. Sound judgment rests the decision about as expressed by Wells.

TABLE 2—*The Increasing Incidence of Carcinoma of the Lung in Particular Institutions*

Compiler and Institution	Period	Percentage of Carcinoma of Lung in All Autopsies	Percentage of Carcinoma of Lung in All Types of Carcinoma
Reinhold (Dresden), Wolf (Dresden)	1852-1876	0.057	
	1877-1884	0.21	
	1885-1894	0.428	
Kikuth (Hamburg-Eppendorf)	1889-1899	0.07	
	1900-1911	0.39	
	1912-1923	0.7— (?)	
Breckwoldt (Barmbeck-Hamburg)	1914-1919	0.36	3.7
	1920-1925	0.39	2.7
Seyfarth (Leipzig)	1930-1936		5.1
	1907-1913		6.88
	1914-1918		11.23
	1919-1923		8.75
	1st half 1924		15.5
Stahelin (Basel)	1900-1911	0.20	
	1912-1914	0.50	
	1915-1923	0.63	
	1924	0.67	
Holzer (Prague)	1895-1904	0.07	1.04
	1905-1914	0.19	2.36
	1915-1924	0.47	6.69
Barron (Mayo)	1899-1911	0.0	
	1912-1918	0.2	
	1919-1921	0.9	
Assmann (Leipzig)	1900-1906	0.67	5.01
	1907-1913	0.9	6.88
	1914-1918	1.01	11.23
	1919-1922	1.54	9.17
Weller (University of Michigan)	Autopsies		
	1-1,000	0.1	
	1,000-2,000	0.5	
	2,001-2,450	0.8	

There seems to be little doubt that primary cancer of the lung is now a more common disease in Europe and America than it was even ten or fifteen years ago. Perhaps there are changes in the incidence of cancer, independent of the increased age level of the population. I am not by any means sure that changes of habits and occupations may not be having some influence on the incidence of cancer.

If one grants for the time being that the increase in the incidence is in part real, possible factors which may be concerned in this increase will be considered under the head of "Etiology."

*Incidence According to Sex*—Breckwoldt, summarizing sixteen of the more recently reported series of cases of primary carcinoma of the

lungs, found that 807 cases occurred in men and 280 in women. This corresponds to a ratio of 2.8:1. None of the compilers of the sixteen series found a preponderance of cases in women even in relatively small series, and only one (Marchesani) found an equal involvement of the two sexes. In 1913, I collected from the literature and studied a group of eighty-seven cases of microscopically verified primary carcinoma of the larger bronchi. Seventy of the eighty-seven were in men. Due allowance having been made for some preponderance in the number of male patients in the hospitals from which many of the statistics are derived, it is clear that primary carcinoma of the lungs is about three times as frequent in men as in women. It likewise plays a more important rôle in men than in women when compared with carcinoma at other sites. Lubarsch found in a series of 86,216 reports of autopsies collected from all Germany that carcinoma of the lung comprised 8 per cent of all cases of carcinoma in men and only 2.57 per cent of all cases in women. Further studies of great interest can be undertaken to discover whether this predisposition for a given sex is equally evident in all types of carcinoma of the lung.

*Incidence According to Age*—When, in 1913, I plotted the incidence of eighty-five cases of primary carcinoma of the larger bronchi according to the ages of the persons involved, I found the highest point of the curve in the age period from 56 to 60. This highest point represented seventeen cases. A subsequent study of 1,100 microscopically verified cases of operable carcinoma in general showed that when the curve of incidence of this material was corrected for the constantly declining population of aged persons its apex fell in the quinquennium from 58 to 62. From this, it followed that the incidence of bronchial carcinoma according to age was in close accord with that of carcinoma in general.

The larger statistical studies of more recent years reached substantially the same result. Holzer found his cases distributed in periods as follows: from 20 to 30 years, 1, from 30 to 40 years, 10, from 40 to 50 years, 18, from 50 to 60 years, 30, from 60 to 70 years, 12, and from 70 to 80 years, 5.

Breckwoldt found 30 of 47 cases in the period from 50 to 70, with 15 cases in each decade. The cases analyzed by Kikuth were grouped in periods as follows: from 20 to 29 years, 7, from 30 to 39 years, 18, from 40 to 49 years, 49, from 50 to 59 years, 77, from 60 to 69 years, 60, from 70 to 79 years, 30, and at 80 years and over, 5.

In Brunn's grouping of collected cases by twenty-year age periods, the results were: from 1 to 20 years, 7 cases, from 20 to 40 years, 60 cases, from 40 to 60 years, 361 cases, from 60 to 80 years, 144 cases, and at 80 years and over, 4 cases.

To all of these larger series many microscopically unverified cases were admitted. While most cases of carcinoma of the lung occur at



the "cancer age," occasionally cases are seen in the extremes of life, and apparently in about the same relative frequency as cancer of the stomach, the uterus and the breast

*Incidence According to Occupation*—Pulmonary carcinoma affords in the "Schneeberg lung-cancer" what is probably the most extraordinary and at the same time the least understood of all the associations which have been discovered to exist between occupation and the incidence of neoplasms. For centuries it has been known (literature reviewed by Hartwig and Hesse, Arnstein, Uhlig, Rostoski, Saupe and Schmorl and others) that a considerable proportion of the underground workers in the cobalt mines of the Schneeberg district in Saxony have, in each generation, died in middle life from some pulmonary disease. The literature on this condition begins at least as early as 1500. The picture of the disease seems not to have varied through the centuries, being characterized by cough, mucoid, mucopurulent or bloody sputum, progressively increasing dyspnea, loss of weight and strength, tendency to sweating, boring pain in chest or back, and death after a varying period of incapacity. There is no way of ascertaining what proportion of those working developed this condition. From local records, however, it appears that during the latter part of the nineteenth century, when from 500 to 600 men were employed in the mines, the number invalidated or dying from cancer of the lung varied from none to sixteen per year (Uhlig). From 1907 to 1911, local death registers gave diseases of the lungs as the cause of 44 per cent of all the deaths of miners (Arnstein). These must have been minimal figures since there practically were not any autopsies. In recent years the number employed has greatly decreased but there is now more accurate information as to the incidence of the condition in question. In the course of the official investigation (three and a quarter years) which formed the basis of the studies of Thiele, Schmorl, Rostoski and Saupe, 154 miners were studied by the methods of modern clinical diagnosis, including roentgenoscopy. During this same period, twenty-one of these died and for thirteen a diagnosis of carcinoma of the lung was established by autopsy, that is, for 62 per cent. For two of the eight on whom autopsies were not made, the diagnosis of carcinoma of the lung was considered highly probable. When these are included the percentage becomes 71. Two of those in whom carcinoma was found at autopsy had not worked in the mines for many years, although at an earlier period one had been so employed for ten years and the other for seventeen. If these two are excluded as not being 'miners,' together with the two whose cases were not verified by autopsy, there still remain 52 per cent of all the miners examined, whose deaths are chargeable to carcinoma of the lung.

In the course of the same investigation, 362 persons of the same districts, but not employed in the mines, were examined without the finding of a single example of carcinoma of the lung

"Schneeberg lung tumor" was incorrectly interpreted as to its neoplastic type for many years, for the earlier workers believed it to be a "sarcoma," "lymphosarcoma" or "lymphosarcoma fibromatodes," being governed by the same error that has occurred so frequently even in recent years in connection with the undifferentiated type of carcinoma of the lung. Loid, even in 1925 continued to class the Schneeberg tumor as lymphosarcoma. One of the cases studied by Ainstein was a squamous cell-carcinoma, which left no doubt as to its epithelial character. Of the 21 cases examined post mortem which Schmorl found available for study, the condition occurred on the left side in twelve and on the right side in nine. In twelve cases, carcinoma of squamous cell type was found, in seven of which it was cornifying. Six cases were of the type of a relatively undifferentiated carcinoma simplex.

Schmorl concluded as a result of the investigation with which he was associated that cancer of the lung is still endemic in the Schneeberg district, that the condition is one of true epithelial neoplasia, and that it occurs only in the miners themselves or in those in the most intimate contact with the products of the mines. (The various theories as to the etiology of this condition are discussed in the appropriate section under the head "Etiology")

Adequate study has not been made as to the general influence of occupation on the incidence of carcinoma of the lung. Seyfarth noted that it is almost exclusively a disease of laborers and handworkers, occurring with special frequency among cigar makers, metal workers, type setters and printers. Five of Kikuth's 246 cases were in cigar makers. To this list Marchesani and others have added cases in coal miners and coal mine laborers, sand stone workers, felters, etc. One can pick out from the lists of cases in persons of known occupation those which may be of significance, but at present a method of evaluating such isolated observations has not been devised. Such cases as that reported by Boyd in a bottle-blower or those described by Beck, Georgi and Wolf in blacksmiths, by Handford in a collier, by Geipel in a cigar maker, by Scott in a chemist in a smelter, by Bryan in a laborer in a smelter, by Kikuth in a chemist, by Fuller in a laborer in a gas works and by Gutzeit in a glass maker may well be of significance. Klotz found that most of the twenty-four cases of which he had personal knowledge occurred in members of the laboring class engaged in diverse occupations. One was in a miner, two were in glass workers and another was in a metal polisher. One gains the impression that such laborers and artisans are especially predisposed, and that members of the learned professions are relatively immune in respect to carcinoma of the lung.

## ETIOLOGY

It is not possible to arrange an ideal classification to include all of the possibly predisposing factors which have been thought to influence the occurrence of primary carcinoma of the lung. In a rather rough way, those which have been suggested may be grouped under the following five heads: tuberculosis, mechanical trauma, acute and chronic infections, fibroid pneumonia and bronchiectasis, of bacterial origin, chronic irritation, chemical, mechanical, thermal and radioactive, and intrinsic predisposition.

*Tuberculosis*—This condition should be given separate consideration, because it was early considered the chief etiologic factor, and Ewing still states that such is the case. This belief was established by Wolf's series in which 13 of 31 cases were associated with tuberculosis and has been kept alive by occasional examples of squamous cell carcinoma arising in bronchiectatic cavities associated with chronic pulmonary tuberculosis, such as the early observation of Friedlander, and by other examples of the coincidence of the two conditions. A rather impressive list of examples of the latter type could be compiled from the literature (reviewed by Kikuth), but it must be borne in mind that two conditions which are so common must often be concomitant without implying a causal relationship. It is significant that carcinoma of the lung appears to be increasing at a time when pulmonary tuberculosis is decreasing throughout the civilized world. Kikuth found tuberculosis mentioned but 22 times in his series of reports of 246 cases of primary carcinoma of the lung. This is roughly in accord with the known incidence of tuberculosis in unselected series. Kikuth felt that tuberculosis plays a small rôle, if any, in determining a malignant pulmonary condition, occupying in this respect exactly the same position as a considerable number of other chronic inflammatory diseases. This is the prevailing opinion at the present time.

*External Mechanical Trauma*—Aufrecht considered severe trauma which "does not produce laceration of the pulmonary tissue, but only molecular disturbances of an unknown character" to be an important immediate cause of pulmonary carcinoma. Four cases which he had seen were preceded by grave trauma. One woman died of carcinoma of the right lung sixteen months after falling from a ladder and striking the right side of the chest. A man accidentally received the full weight of a beam, which he was assisting in lifting, on his left shoulder. Two years later he died of diffuse carcinoma of the upper lobe of the left lung. Georgi's blacksmith was hit on the chest by a heavy mass of iron. The third patient described by Scott and Forman had suffered severe contusions of the chest when caught in a belt. The carcinoma, however, developed on the opposite side. In Barron's fifth case the patient gave

a history of a fall from a ladder, striking the chest on a plank, shortly before the onset of pulmonary symptoms. Similar examples are to be found here and there throughout the literature (Hinteistoissen, Handford) but they are so few that one must conclude, contrary to Aufrecht, that a single episode of external mechanical trauma is practically not of importance in determining carcinoma of the lung.

*Acute and Chronic Infections Fibroid Pneumonia and Bronchiectasis, of Bacterial Origin*—The apparent rise in incidence of malignant pulmonary conditions following the great influenza epidemic of 1919-1920 attracted attention to a possible causal relationship between the two conditions. Meyer does not hesitate to explain his case thus. As will be pointed out under the head "Histogenesis," metaplasia of the bronchial epithelium to the squamous cell type is an undoubted forerunner of bronchial carcinoma in certain cases. Mittasch, Askanazy and others have found such changes in cases of influenza, but Koopmann did not find a single case of epithelial metaplasia or of atypical proliferation in a relatively large series. Whatever effect influenza may have would seem, therefore, to depend on chronic inflammatory processes, residual to the sequelae of influenza, rather than on influenza itself. Nevertheless, as I know from personal experience, it is the custom in certain European institutes to assign the apparent increase in the number of cases of carcinoma of the lung to this one cause. There is good evidence to show that its effect cannot be very weighty. Kikuth found reference to a preceding influenza in only 21 of 246 reports of cases of carcinoma, and in these the interval of time intervening varied from three months to ten years and over. The literature dealing with this question is concisely reviewed by Hueper. He pointed out that no similar increase was noted after the pandemic influenza of 1889-1894, that the present trend of increase was already apparent before 1919-1920, that even the most enthusiastic advocates are unable to show any considerable incidence of "influenza" for their cases of carcinoma of the lung, and finally that the contrast between the two conditions in respect to incidence according to sex is an important objection to this theory.

The sequelae of influenza, however, so far as they bring about bronchiectasis or chronic fibroid pneumonia, are of importance. There are many examples of carcinoma of squamous cell type, arising in bronchiectatic cavities, a few in supposed syphilitic scars (Ziemssen) and several in areas of fibrosis. The writer has seen carcinoma of the lung in association with chronic fibroid pneumonia in which the transition pictures between the regenerated bronchiolar epithelium (cells of Tripier) and undoubted neoplasm did not leave any question of the origin of the malignant process in the area of induration. Such chronic

inflammatory conditions as are accompanied by metaplasia or excessive regeneration must be included among the predisposing factors

*Chronic Irritation, Mechanical, Chemical, Thermal and Radioactive*—In considering this group of factors, which have assumed great importance in the last few years, attention must first be directed to two lines of evidence which are instructive in their bearing on the whole problem. The first of these has to do with the many theories which have been advanced to explain the etiology of the carcinoma of the lung in the miners of the Schneeberg. The theories show how complex, in reality, is an industrial hazard which appears to be of relatively simple solution. What environmental factor predisposes the Schneeberg miners to carcinoma of the lung? This subject has recently been thoroughly reviewed by Rostoski, Saupe and Schmoil. In part, these mines are damp and show abundant growth of both microscopic and larger fungi. The men are compelled to climb up and down ladders for considerable distances, in some instances for as much as a thousand feet. In the harder rock, where drilling is necessary, a fine stone dust is produced in quantity. The ore contains iron, bismuth, tin, zinc, lead, manganese, uranium, cobalt and nickel, chiefly in combination with sulphur and arsenic. The ore is also radioactive. Thus the situation affords the possibility of mechanically irritating stone dust, chemically active dusts, particularly arsenic, the possibility of inhalation of arsine, diethylarsine, or other volatile arsenic compounds, perhaps produced by the flora of the damp mines, and the inhalation of a radioactive substance. The rock dust actually has at times a content of arsenic of nearly 0.5 per cent and prolonged contact with it leads to a chronic eczema. The air of the mines has a radioactive emanation content of from a few to 50 Mache units. Schmoil felt that the anthracochalcosis found in the lungs of these miners must be of significance. Pneumokoniosis was demonstrated by the x-ray in many of the living. Yet such a mechanical irritation fails to explain why in this group of mines, alone, carcinoma of the lung has been prevalent for centuries. The final answer is still to be sought. Sanitary measures looking toward a reduction of the dust hazard seem already to have effected some reduction in the incidence of the disease. The mines, however, are now being worked on a much smaller scale.

The second line of evidence to which attention must be called is the experimental production of new growths in the lungs of laboratory animals. Following the introduction of dilute hydrochloric acid into the bronchial tree, Winternitz, Smith and McNamara found that an "overproduction of the epithelium occurs and may form bronchiolar polyp or extend into the peribronchial tissue" producing a picture which "may easily be confused with that of a malignant neoplasm." This is probably the basis of a statement frequently quoted in the German literature that

bronchial carcinoma was thus produced by them (Joannović) Kimura quotes Ibuka as having introduced pieces of paraffin into the lungs of rabbits. These became encapsulated by much scar tissue in which, in three instances, epithelial tubular and alveolar structures were formed, but not anything that could be interpreted as cancer. Block and Dreifuss, in 1922, were successful in producing skin carcoids in mice by "tarring." Four fifths of the mice with the skin carcoids showed metastases to the lung. Two or three mice presented, in addition, adenomatous tumors of the lung of the usual type, but these were thought to be spontaneous and not in any sense due to the tar and tar derivatives which were being tested.

By intrabronchial insufflation of coal tar, Kimura produced in the lung of a rabbit a small, circumscribed nodule consisting of twisted tubules lined by an epithelium of cylindric cells, an adenoma-like growth. In a guinea-pig which had been thus treated and killed on the 140th day, multiple nodules were found in the lungs. One hard mass, of the size of a large pea, was composed of groups of epithelial cells with a glandular architecture. Bronchi and bronchioles were embedded in the tumor mass. The epithelial lining of these bronchi was several times as thick as the normal lining and there were polypoid ingrowths partially occupying the lumen. The boundary of the mass was not well defined, and it seemed to infiltrate the surrounding lung tissue in a radiating manner. This was interpreted as adenocarcinoma of bronchial origin, produced by chemical stimulation alone, in an animal possessed of a special predisposition.

Murphy and Sturm endeavored to eliminate the criticism that the tumors of the lung in tarred animals are but the metastases of unrecognized primary carcinoma of the skin by applying the tar to twelve different areas on each mouse. Tumors of the lung of the usual type for mice were found in 60 per cent of the animals in one series and in 78.3 per cent in another. "Control mice from the same stock, but from three to six months older, and for that reason the more liable to spontaneous lung tumors, failed to show a single instance of such growths." It was believed that the inhalation of particles of tar could be ruled out as a cause.

In 1925, Moller produced in 6 of 24 rats, treated on the skin of the back with tar, primary cornifying squamous-cell tumors of the lungs. All of the rats, and those only, which survived to receive treatment for 300 days or more, developed these growths. Microscopic examination of the treated areas of the skin failed to show a neoplasm.

In thirty-one mice dusted daily or every other day with a dried pulverized tar gum arabic emulsion, and 104 mice which were tracheotomized and into which a fresh tar gum arabic emulsion was injected (once only) intratracheally, Bonne did not find a definite increase in

the incidence of tumors as compared with untreated animals. One of twenty rats varied about the mouth twice weekly for twenty weeks was found to have two nodules the size of pinheads at a lung border. Histologically, these were cornifying squamous cell carcinomas. Association with a bronchus could not be demonstrated.

In the present year (1928), Willis and Brutsaert have described tumor-like structures in the lungs of guinea-pigs exposed to silica dust. In 7 of 80 guinea-pigs which were exposed for from eighteen to thirty-one months for periods totaling about fifty hours a month to the inhalation of a dust which was 98 per cent silicon carbide, remarkable peribronchial proliferations were found. These appeared to be derived from both bronchial and alveolar epithelium and were found only in the "dusted" animals. Positive evidence of adenocarcinoma character was lacking.

From this survey it may be seen that some success has been obtained in producing tumor-like structures in the lungs of laboratory animals, particularly mice. Tar and tar derivatives have been the most successful aids in bringing this about.

Returning to a consideration of the etiology of carcinoma of the lung in man, one finds that a great variety of irritative agents have been suggested. Space does not permit a review of the discussion, pro and con, which has developed in respect to each of these. The first was anthracosis, early suggested by Wolf as being important in connection with the breaking through to the bronchial mucosa of pigment-laden bronchial nodes. Industrial dusts have also received much attention, particularly, among the organic dusts, tobacco. The number of cigar-makers affected by pulmonary carcinoma has seemed disproportionate to the number engaged. Of the inorganic dusts, the silicates (silicosis) have been especially considered, and certain industrial metallic dusts. On the importance of excessive cigarette smoking, Fahr is quoted by Hueper. Perret and others have been struck by histories of excessive use of tobacco in their patients. If this be the true explanation, there should be an alteration of the present ratio of the incidence in men to that in women within the next decade or two. Specific chemical fumes seem to have played a part in many cases. Chemists and those working about smelters appear rather frequently in the lists of cases of carcinoma that have been classified according to occupation of the persons involved. Kikuth was much impressed by the case of a young man aged 39, previously healthy, who died of bronchial carcinoma fourteen months after going to work in a chemical factory in which he was exposed to heavy fumes containing dichlorethylene, trichlorethylene, pentachlorethane and hexachlorethane. The gassing of men in the war has also been considered a factor in increasing the incidence, and in view of the coincidence of the increase in the incidence of carcinoma of

the lung with the increase in the use of automotive vehicles, the products of the incomplete oxidation of gasoline and other motor fuels must be included among the possible etiologic factors. Stahelin has investigated particularly the use of tar and heavy oils in laying street dust, since particles coated with these materials must be constantly inspired in the course of the abrasion of such roads. Here there is an important field for further study. At present, it is not clear that there is any close parallelism in various cities between such laying of dust and malignant conditions of the lungs. The diagnostic and therapeutic use of the x-ray has been considered, but it seems rather clear that this can be dismissed as a causative factor, although important in centralizing these cases in institutions. Discussions of these factors with reference to the views of the chief proponents of each can be found in articles by Kikuth, Beiblinger, Hueper, Stahelin, Marchesani, McCrae, Klotz and others. In a general article on neoplasia of irritative origin, Joannovic wrote in regard to the group under discussion:

The more or less constant inhalation of finely divided vegetable dust appears to be the cause of cancer of the respiratory tract in cattle, sheep and horses. The remarkable increase in pulmonary cancer in man has been variously ascribed by authors to metaplastic epithelial proliferations secondary to influenza, to war-gassing and to the abuse of cigarette smoking. Upon the ground of various observations one is more and more inclined to attribute to the inhalation of dust and the resulting pneumokoniosis a greater significance in the origin of pulmonary cancer.

Final conclusions cannot be drawn at present, but many interesting fields have been opened for further study.

*Intrinsic Predisposition*—Most writers on the subject dismiss with a brief negation the possibility that an inherited predisposition is of importance in the etiology of carcinoma of the lung. That this should not have received fuller consideration is all the more remarkable since the tumors of the lung in mice have played an important part in the experimental proof of the importance of hereditary factors as this has been developed by the work of Slye, Tyzzer, Lynch and others. Experimenting pathologists and geneticists, no matter how much they may differ in regard to the mechanism involved and its mendelian implications (recessive, sex-linked dominant, dominant), are agreed that it is possible largely to determine the incidence of tumors of the lungs in mice by proper selective breeding. With this important lead, it is surprising that the reports of cases and the statistical studies of carcinoma of the human lung practically never mention a family history of malignant conditions whether it be negative or positive. There are a few exceptions. For instance, Moise emphasized the strong family history of malignancy in his case 4. The patient was a woman, aged 42, whose father had died of cancer of the liver, paternal grandfather



of cancer of the stomach, a paternal aunt of cancer of the breast, and whose sister had had a renal tumor of unknown nature removed. The father of a patient, a woman 31 years old, described by Bergmark and Quensel, died of intestinal carcinoma at 32. Such reported histories are few, but apparently this point has not been adequately investigated.

*Summary of Etiology with Probable Trend of Opinion*—If one may be permitted to look ahead in the light of recent advances, it may be predicted that the development of carcinoma of the lungs and bronchi will be found to be due (1) to an inheritable intrinsic predisposition which may be activated by (2) a variety of chronic irritative factors. These may be mechanical, chemical, bacterial, thermal or radioactive, but they have in common the ability to incite proliferation of certain cells, regeneration, repair, hyperplasia and often metaplasia. Such extrinsic factors are potent in the production of pulmonary and bronchial carcinoma in varying degrees in different persons depending on the degree of intrinsic predisposition which may be present.

#### GROSS PATHOLOGIC ANATOMY

*Location*—Carcinoma of the lung is, in a majority of instances, carcinoma of a bronchus. "Bronchiogenic carcinoma" has become a common diagnostic phrase with the realization of this fact. Kikuth believed that 179 of the 225 cases studied by him were definitely of bronchial origin. Breckwoldt found 36 of the bronchial form out of a total of 47. The actual proportion is undoubtedly higher, as each of these writers had a fairly large group of doubtful cases, some of which were probably bronchial. In 1913, I collected and reported on a group of carefully selected cases of carcinoma of the larger bronchi, hoping to establish such a definite clinical picture for this condition that it could be set off from the general group. This hope has been realized only partially, on account of the fact that proved cases of nonbronchiogenic carcinoma of the lung are rare indeed. Certainly, the ratio must be as high as ten bronchiogenic to one of other origin.

In the older literature and in textbooks, stress has been laid on a supposed excess of cases of carcinoma in the right lung as compared with the left. Reinhard, for instance, in 1878, reported 18 instances of carcinoma for the right lung and but 9 for the left. This disproportion was attributed to the larger size and more direct course of the right main bronchus in the thought that it would be subjected to a greater degree of chronic irritation than the left. Adler, in his combined list of parenchymal and bronchial neoplasms, found the right side more frequently affected than the left, but thought the difference was too small to serve as a basis for a theory. In more recent statistical studies, the difference between the two sides in respect

to incidence of carcinoma has not been evident Kikuth found the right lung primarily involved in 123 instances, the left in 118, and an equal involvement of both lungs in 5 In summing up 503 unilateral cases, including forty-three of his own, Breckwoldt found the right side primarily involved 273 times, the left, 230 times This slight right preponderance is rather constant in the collected series of recent years, only a few writers—among others, Schmorl with the Schneeberg miners, and Hanf—seriously differing The latter found 95 cases of carcinoma of the left lung to 72 of the right In the compiled series of McCrae, Funk and Jackson there was a slight preponderance of cases of carcinoma of the left lung Brunn found, on combining 252 additional cases, chiefly from the literature, with Adler's list of 374, that 283 were said to be of the right side, 246 of the left side, 26 of both sides, with 3 doubtful and 68 in regard to which no statement as to side was made

As to lobar distribution, a grouping which necessarily excludes many tumors of the hilum, Kikuth found the right upper and middle lobes involved 38 times, the right lower lobe, 35 times, the left upper lobe, 31 times, and the left lower lobe, 30 times In addition, there were 49 instances in which all three lobes on the right were involved and 57 in which both lobes of the left lung were involved Breckwoldt likewise found the right upper lobe to be involved slightly more frequently than any other single lobe

*Types*—Numerous classifications of carcinomas of the lung have been proposed A survey in the light of the hundreds of reports of cases now available shows that from the standpoint of gross pathology, three types must be considered a type associated with the hilum, a nodular type developing in the parenchyma of a lobe and a diffuse type Evidence is lacking that the alleged primary miliar carcinoma reported by certain writers is other than metastatic miliar carcinomatosis with an undiscovered primary Pleuritis carcinomatosa (Bergmark and Quensel) is but a manifestation of carcinoma arising elsewhere, either within the lung or outside of it This grouping agrees as to its three main types with that proposed by Fishberg for his series of neoplasms of the lungs

The type of carcinoma that occurs in the hilum, comprising perhaps 90 per cent of all cases of carcinoma of the lung, is practically always bronchiogenic It may arise in a main bronchus at or near the bifurcation and thus be originally outside of the boundary of the lung itself A frequent site is in the main bronchus near the mouth of the first lobal branch (Kikuth) The gross appearances as seen from the lumen are exceedingly variable, ranging from a roughening of the mucosa, through various types of intrabronchial polypoid masses (literature reviewed by Kirch) to complete bronchial stenosis, which is not infrequently present

when the condition is seen at autopsy. In the bronchial wall, the neoplasm infiltrates widely, extending along the bronchial tree and radiating into the substance of the lung and also into the mediastinum. Death may occur while an intrabronchial mass is still small or only when an enormous neoplasm fills the mediastinum and nearly completely replaces the lung. With the more massive examples of this type, the bronchi, when cut across, are found completely infiltrated and their lumina plugged. The neoplasm is usually firm in consistency, except where showing secondary necrosis, and is yellowish white. With secondary infection or extensive necrosis, cavitation of the neoplasm occurs.

The nodular type, developing in the substance of a lobe, is much less common, yet there are many descriptions of it in the literature. When such nodules are described as multiple, there must always be some suspicion that the condition is not primary in the lung. Certain cases, however, seem well authenticated. Schmoil saw multiple foci of origin in one or two of the Schneeberg cases which he investigated. McMahon and Carman found multiple nodules in both lungs of one of their patients (109685) and did not find any evidence of a primary growth outside of the lung. Such a picture might be explained as one of intrapulmonary metastasis from a single primary. Another possible source of error in connection with this variety can be illustrated by Brunn's second case in which x-ray showed a circular tumor-like mass in the lung in the left infraclavicular region. This was removed and diagnosed as papillary adenocarcinoma. At autopsy ten days later, a small tumor practically filling a bronchus near the root of the lung was discovered, but the apical mass was nevertheless considered to be the primary tumor. It seems more probable that the tumor in the hilum was the original one. As will be pointed out later, the lobar situation of a carcinoma does not exclude a bronchial origin. A tumor described by Edlavitch lay chiefly in the right apex, bulging the clavicle forward, yet it was of undoubted bronchial origin.

An extensive literature has arisen in respect to the diffuse type, which is frequently bilateral. Here, again, suspicion is justifiable that the pulmonary condition may be metastatic from a hidden primary, but there are now many cases which have been well studied so that this type must be given serious consideration. The unilateral manifestation of this condition can be illustrated by the instance observed by Gordon. The patient was a woman, aged 56, who had had for four months a cough, dyspnea, a little expectoration, but no hemoptysis. At autopsy, all of the right lung with the exception of the inferior portion of the lower lobe was found infiltrated with a homogeneous mass.

Grossly, the condition looked like the gray hepatization stage of croupous pneumonia. Signs of disease were absent in the other organs.

Microscopically, each alveolus was found to be filled with a "papillomatous collection of columnar epithelial cells arranged on a delicate fibrous support of dendritic structure" The bronchi were unaffected

The bilateral form of this type was described by Musser in 1903 as it was found in a man, aged 47 "Uniformly throughout both lungs, affecting all parts, is a diffuse grayish-yellow infiltration" Microscopically, the alveolar architecture of the lung was more or less retained and papillary ingrowths covered with cubical or columnar cells were everywhere found projecting into the alveoli Prostate, thyroid and all other organs were examined without finding a primary outside of the lung Bryan, Eismayer, Briese and many others have described similar examples Briese reviewed a number of additional cases falling into this group The case described by Hyde and Holmes gave clinical and roentgenologic evidence of involvement of the right side first, while at autopsy, eight months later, both lungs were found to be extensively infiltrated with no evidence of an extrapulmonary primary This case affords a possible explanation of the bilateral form of the diffuse type, for metastatic dissemination throughout the lungs seems more probable than does such extensive multicentric origin

Forms representing transitions between these three main types are occasionally encountered, and when the neoplasm has infiltrated extensively it may be difficult of classification

*Regional Extension*—Particularly in the type associated with the hilum the mediastinal extensions become important Certain structures are involved with great frequency The pericardium and heart are more frequently infiltrated when bronchiogenic carcinoma is present than in the case of any other form of neoplasm Brunn found the heart involved in 21 per cent of 626 reported cases In the literature, the process is frequently called metastasis but it is usually a direct extension through the pericardium, in the perivascular lymphatics or along the lumina of the great vessels themselves A frequent reference in the literature is that to a polypoid neoplastic mass protruding into the right auricle from the mouth of the superior vena cava or into the left from a pulmonary vein The myocardium may be infiltrated nearly to the apex (Young)

An extension to the great vessels of the thorax is also common It may occur as a compression and infiltration of the wall, or more commonly as a so-called neoplastic thrombus filling the lumen The superior vena cava, the pulmonary veins and the pulmonary arteries are most frequently concerned Caval obstruction leads to vascular changes, to be described shortly Several cases are reported in which death occurred through massive hemorrhage from an eroded pulmonary artery (Kikuth, Moses, Bruecken discussing the paper of Dever and Royce)

The esophagus is frequently compressed and infiltrated, usually in its middle third This may produce marked dysphagia The compres-

sion of the trachea gives the "cornage" sign of the French. The compression and infiltration of regional nerves leads to recurrent laryngeal paralysis, to pupillary inequality and to pain along the intercostals. The frequency of the involvement of the nerves is shown by the fact that thoracic, abdominal or back pain occurs in over 50 per cent of all cases.

A direct extension to the thoracic wall is more rare. Bluecken, in discussing the paper of Dever and Royce, described a patient on whom a diagnosis of gumma of the sternum, and later of sarcoma of the sternum had been made. Autopsy showed this lesion to be a direct extension of a squamous-cell carcinoma of the right bronchus. Kikuth found a mass the size of an apple in the left pectoralis muscle in continuity with a primary carcinoma of the lung.

*Metastasis*—Carcinoma of the lung rarely fails to produce metastases. In the series compiled by Klotz, metastasis was absent in only one instance and Bieckwoldt found metastases in 37 of 43 cases. The regional lymph nodes are involved in practically all cases—the bronchial, supraclavicular, cervical and axillary. In many cases, the removal of a node for microscopic examination has confirmed the diagnosis. After the regional nodes, Kikuth found metastases to be distributed to the other organs, in his series of 246 cases, as follows: liver, 70, skeleton, 48, lungs, 43, brain, 31, kidney, 25 (left, 9, right, 4, both, 12), suprarenals, 21 (left, 8, right, 4, both, 9), pancreas, 11, thyroid, 5, heart muscle, 4, intestines, 3, stomach, 2, spleen, 2, gallbladder, 1, and ovary, 1.

Dosquet has studied the distribution of the metastases from primary carcinoma of the lung, including bronchial carcinoma, from the standpoint of the preponderance of suprarenal and central nervous system metastases, which this condition produces. He found in a group of 105 cases of carcinoma of the lung that 31.4 per cent showed metastases to the central nervous system and 21.8 per cent suprarenal metastases. When other forms of cancer were brought into comparison, 2,158 cases showed 0.9 per cent with metastases to the central nervous system when the lung was not involved, and 1.6 per cent when the lung was involved, a total of but 2.5 per cent. Similarly, the same 2,158 cases of carcinoma yielded 1.9 per cent with suprarenal metastases when the lung was not involved, and 2.6 per cent when the lung was involved, a total of 4.5 per cent.

The frequency of metastases to the central nervous system as found at autopsy (Fried) is paralleled by the frequency of clinical cases in which such metastases dominate the picture and lead to erroneous diagnoses. Apoplexy and tumor of the brain (Lubarsch) have frequently been diagnosed, sometimes on the basis of hemiplegia.

The skeletal metastases have never been fully studied, and their importance should be emphasized. In the usual autopsy, most

bone metastases escape detection. A suddenly developing vertebral deformity, as in the thirteenth case in Bailon's list, may be the first indication of such a disease. The Department of Pathology of the University of Michigan has in its series a similar example in a patient with a diagnosis of Pott's disease, which proved to be metastatic carcinoma from the lung.

*Changes in the Lung, Peripheral to the Carcinoma*—The common bronchiogenic type is often accompanied with important changes in the lung, peripheral to the neoplasm. These are determined largely by the degree of obstruction and, when present, they influence the physical signs of the disease. With a polypoid growth into the bronchus, a ball-valve action may be present, so that there is emphysema peripheral to the neoplasm. Atelectasis due to obstruction is more common. Korner described a case of atelectasis due to a complete obstruction of the entire right lung by a bronchiogenic carcinoma, which was present, moreover, for seven weeks before the death of the patient. In a personal communication, C. H. Cocke provided me with notes on another as yet unpublished case of massive collapse of the right lung due to a malignant endobronchial neoplasm. Bronchiectasis with chronic purulent bronchitis frequently occurs beyond the region of the neoplasm, and an entire lobe or the greater part of the lobe may show a chronic fibroid pneumonia.

*Pleural Effusion*—The pleura is usually involved in the carcinomatous infiltration by the time death occurs. There may be a general pleuritis carcinomatosa, as described by Bergmark and Quensel, or the pleural involvement may be more nodular in type. Kikuth found in more than half of his cases an exudative pleuritis, which was of a hemorrhagic character (twenty-eight instances). Diagnosis from cells in the pleural fluid is discussed in a subsequent section.

*Vascular Phenomena*—Changes in the flow of the blood and the lymph, particularly of the upper part of the body, are responsible for an interesting chapter in the pathology of carcinoma of the lung. These depend on compression, infiltration and blocking of the greater thoracic vessels by the tumor. The inequality of radial pulses may be due either to intrathoracic pressure from the primary tumor or to axillary metastases. Its presence may induce an incorrect diagnosis of aortic aneurism. Venous engorgement, often with marked cyanosis and edema, is more common. Fishberg's experience was unusual, for he saw such signs of distant pressure in but 2 of 60 cases of primary malignant disease of the bronchi, lungs and pleura. In 90 reported cases taken at random from the literature, some of which were incompletely described, I found such venous phenomena referred to 8 times. Nonnenbruch emphasized unilateral inspiratory distention of the veins of the neck as a diagnostic sign of stenosis due to bronchial carcinoma. This sign is

observed on the side opposite the neoplasm Dana and McIntosh, in 1922, surveyed the diagnostic significance of venous obstruction in carcinoma of the lung, particularly in respect to the superior vena cava The seat of the malignancy was found to be in the right lung or bronchus in most of these cases One patient in my own series showed an extraordinary distention of the superficial collateral veins of the anterior thoracic and abdominal wall At autopsy, a tumor was found completely blocking the superior vena cava

*Clubbing of the Fingers, Osteo-arthropathy*—In 1915, Locke concluded that simple clubbing of the fingers and secondary hypertrophic osteo-arthropathy should be considered as identical, the former representing an early stage of the latter The occurrence of all degrees of this condition in association with a malignant condition of the lung is in accord with this view Teleky, in 1897, included carcinoma of the lung in his list of causes of "osteopathie hypertrophique pneumique" In a case described by Ash, there was the full picture of chronic hypertrophic osteo-arthropathy with enormous clubbing of the fingers and toes Additional cases can be found described in the papers of Braun, Brunn, Koinblum, Packard, Young and many others I found reference to some degree of this condition 13 times in 90 reports of cases selected at random from the more recent literature Brunn emphasized the importance of careful examination of the pituitary body in all cases of carcinoma of the lung with osteo-arthropathy Braun actually did find a metastasis in the anterior lobe in such a case, and others have described a general hyperplasia of that lobe in osteo-arthropathy associated with pulmonary carcinoma

#### MICROSCOPIC PATHOLOGIC ANATOMY

For discussions of the microscopic pathology of carcinoma of the lung, reference may be made to such general articles as those of Barron, Breckwolft, Briese, Eismayer and Marchesani

Probably not another regional carcinoma exhibits so wide a range of architecture as the one under consideration All possible structural and cellular types are found, from scirrhous and diffuse medullary forms through less fully developed acinar and glandular structures to papilliferous cystadenocarcinoma with elaborate dendritic processes extending into the cystic spaces There is no agreement in statistical studies as to the percentage of each structural type In general, it may be stated that in the earlier statistics the adenocarcinomatous group was considered to be much the more abundant, while in recent studies the recognition of certain undifferentiated types as carcinoma and not sarcoma has increased the scirrhous and medullary divisions As a matter of fact, the available material does not lend itself to analysis from this standpoint, since, in reports of cases, glandlike architecture is usually fully

described, while that of the undifferentiated and squamous cell varieties is left to be inferred, particularly as regards the proportion between carcinoma cells and stroma

Most carcinomas of the lung, as to cell type, can be assigned a place in the following classification undifferentiated cell carcinoma, squamous cell carcinoma, and cylindric cell carcinoma

This general grouping differs somewhat from that of Marchesani, which was also used by Bieckwoldt They recognized four types basal cell carcinoma, polymorphous cell carcinoma, cornifying squamous cell carcinoma and cylindric celled adenocarcinoma

My modification is made on the grounds that the prototype of the undifferentiated cell usually cannot be made out, that it may have come originally from either a squamous or a gland cell epithelium, and that the conception of cylindric cell mucosae having basal cells has never in this country gained a firm footing

Satisfactory figures are not available in regard to the incidence of the various cell types Differences in individual opinion, the existence of intermediate types, and especially the fact that the degree of differentiation may vary in different portions of the same neoplasm have hindered such studies Barron found the cylindric cell carcinoma the most common, Henrici found but twelve of the squamous cell type among eighty-five collected from the literature Among fifty-seven selected cases of bronchiogenic carcinoma reported in the literature, I found twenty-five that were stated to be squamous celled, twenty cylindric, cuboidal or gland celled, and ten polymorphous, round or oval celled

The carcinomas of the lung which may be grouped as of undifferentiated cell type have only of late received a proper interpretation Formerly they were called sarcomas Adam appreciated this difficulty and wavered between a diagnosis of carcinoma and one of sarcoma in his case reported in 1895-1896 Von Glahn's eighth case, which he finally styled "alveolar sarcoma or preferably a mesothelioma arising from the pleura," was undoubtedly of this type It is now known that, apart from lymphosarcoma of the lymphoid apparatus, primary sarcoma of the lung is one of the rarest of blastomas (Ewing) Architecturally, such carcinomas are usually described as carcinoma solidum, or medullary carcinoma, sometimes as scirrhous They occur at the hilum of the lung in almost all cases and spread extensively in the mediastinum and over the pleura, where they have been erroneously counted as "mesotheliomas" They may be composed of very small cells with scant cytoplasm, inviting confusion with lymphoblastoma, or of large round cells, polyhedral, or even, in part, spindle cells, as Ewing stated

Carcinoma composed of squamous cells may be either cornifying or noncornifying The cornifying type presents no difficulty in classification as to cellular structure and therefore ranks high in statistics pre-



pared from reports of single cases. There are many reports of this type throughout the literature (Einstein, Meyer, Moise, Peils, von Glahn and others). The noncornifying type merges, in its less differentiated forms, with certain types characterized by polymorphous and so-called basal cells. It probably goes unrecognized rather often. It occurs much more frequently than the cornifying type.

The type in which cylindric cells prevail is highly variable. In its most completely differentiated form, the cells may be ciliated and borne on a branching papillomatous stroma proceeding into dilated alveolar spaces. The papillomatous structure appears in most instances of carcinoma of the lung of the diffuse type, to which reference has been previously made. Forms made up of lower cylindric and cubical cells occur, likewise, all intermediate forms between a clearcut adenocarcinoma, an acinar structure with solid nests of cells, and a medullary or even scirrhous carcinoma. With the various forms built of cylindric cells the question of the formation of mucin always arises. True epithelial formation of mucin has been demonstrated repeatedly by specific stains. The mucin may be so abundant as to be released in quantity in alveolar spaces, or it may be retained in dioplet form within neoplasm cells of "signet-ring" type.

#### HISTOGENESIS

Much of the effort which has gone into the study of carcinoma of the lung has been expended in endeavoring to settle problems of histogenesis. This question, which, alone, would provide material for an extensive general review, can be presented only briefly here. The discussions by Feyrter, Meyer, Eismayer and Marchesani give the more recent views on this subject. Practically every case reporter has reached an opinion in regard to whether the origin of his case should be assigned to the bronchial mucosa, the bronchial mucous glands or the alveolar epithelium. Such decisions have been based on (1) position of the growth in the lung, (2) behavior in respect to various structures of the lung, and (3) cell type, including cell products, such as mucin.

As to position in the lung, it can be asserted that those growths which are grossly of the type associated with the hilum have their origin in bronchial structures, either the mucosa or the mucous glands. It cannot be assumed, on the other hand, that those found well out in the lung are of alveolar epithelial origin. Such tumors may arise from the epithelium of the smaller bronchi or from the cubical epithelium of an attempted regeneration (cells of Triplett), which is bronchiolar rather than alveolar.

As to the manner of growth, particularly in relation to the structures of the lung, it has been assumed that the neoplasms which are diffuse

throughout a lobe or lung, covering the alveolar walls, are the result of direct origin from the alveolar epithelium. Boecker showed that the architecture of the tumor which he described could be explained as a progressive growth from alveolus to alveolus, which utilized the original stroma as the neoplasm spread. Henrici expressed the same opinion in 1912. A polypoid or papillomatous growth into the lumen of a bronchus, or an irregular thickening and roughening of the mucosa, may indicate an origin from the bronchial epithelium, if an extensive infiltration around the bronchus is not present also. A marked peribronchial growth with early stenosis has been thought to imply an origin in the bronchial mucous gland.

On the type of cell of which the neoplasm is composed, alone, in many cases, an opinion has been founded as to the histogenesis of a carcinoma of the lung. In the early literature, a neoplasm made up of squamous cells was often assigned an alveolar epithelial origin with apparently not a reason other than that its cells were flattened. Especially tall columnar cells were considered to indicate an origin from the bronchial epithelium, and a formation of mucin to signify a neoplasm arising in the mucous glands. It is only now beginning to be understood generally that the type of cells of which the carcinoma of the lung is constituted is much more an indication of the degree of differentiation than of the precise histogenesis. As Klotz and others have pointed out, the epitheliums of the bronchi, bronchioles and respiratory alveoli have a common parentage and must be possessed of similar potentialities of differentiation or lack thereof. A broader view of the biologic aspects of the whole question shows how impossible it is to ascertain the origin of carcinoma of the lung by identification of its type of cells, alone. It has repeatedly been pointed out that different parts of the same neoplasm may show entirely different types of cellular organization. There are not only different degrees of anaplasia for different neoplasms, but also variations in the degree of differentiation throughout the life history of a given neoplasm for different areas of its growth.

The relationship of the cornifying squamous cell carcinoma to metaplasia is firmly established. Some writers prefer to follow Goldzieher in considering the change in cell type a "basal cell proliferation with partial differentiation" rather than a true metaplasia. Haythorn, Askanazy and others have shown that such a change in the lower tracheal and bronchial mucosa is of frequent occurrence. Bronchiectatic cavities are especially apt to show it. The frequent origin of carcinoma formed of squamous cells in such cavities thus finds a ready explanation. This type of carcinoma may arise, in a peripheral position in the lung, from small bronchi, bronchioles or possibly alveolar epithelium.

Summing up present day opinion in regard to the histogenesis of carcinoma of the lung, it is clear that most cases are regarded as of bronchial origin, and that proof of the origin of carcinoma of the lung from histologically unaltered alveolar epithelium is lacking. The cyto-architecture reveals the degree of differentiation and not the histogenesis. The formation of mucin does not prove origin from the bronchial mucous glands, but the manner of growth and the character of the bronchial mucosa may serve to differentiate between carcinoma originating in the mucous glands and carcinoma originating in the bronchial mucosa. The histogenesis of the type formed of squamous cells as following metaplasia is fully accepted.

Most carcinomas of the lung are too far advanced when seen to give any sure indication of their origin. As Marchesani suggests, systematic studies postmortem should in time provide examples of early stages of carcinoma of the lung in patients dying of other diseases. Only by such chance opportunities can some of the questions of histogenesis be answered.

#### THE PATHOLOGIST IN THE DIAGNOSIS OF CARCINOMA OF THE LUNG INTRA VITAM

Considerations of the symptomatology, the diagnosis and the treatment of carcinoma of the lung are outside of the limits imposed by the title of this review. A reference must be made, however, to the assistance which the pathologist may render in the diagnosis of the condition *intra vitam*.

Since carcinoma of the lung is usually carcinoma of the larger bronchi, skillful bronchoscopy becomes, in selected cases, the most useful procedure in making a diagnosis (Killian, Jackson, et al., McCrae, Funk and Jackson). Not only does the bronchoscopist learn much from the form, color and movement of the bronchi but he frequently finds it practicable to remove a portion of an intrabronchial growth for biopsy. The pathologist may thus have an opportunity to see bronchial carcinoma in a relatively early stage. Benign polypoid growths must be excluded. Examples of malignant growths thus diagnosed after biopsy may be found in reports by Jackson and his associates, Hyde and Holmes, Ephraim and others.

In the second place, biopsy of secondarily involved lymph nodes enables the pathologist to determine the presence of malignancy and also its general type. With the help of a careful physical examination and roentgenoscopy the diagnosis may thus be established.

The sputum resembling currant-jelly or raspberry-jelly described by the earlier writers is rarely seen (Hampeln), although a streaking with blood or even an abundant hemorrhage is common in the later course of the disease. The pathologist may, on rare occasions, make

a diagnosis from fragments of the tumor discovered in the sputum Betschaert reported the diagnosis of pulmonary carcinoma by this method in 1895 and reviewed the scant literature on the subject, which revealed three previous cases Pfahler reported a diagnosis similarly obtained in discussing Bijan's paper, and Barker's patient twice coughed up masses of tissue The second specimen was examined and it led to a diagnosis of squamous cell carcinoma

Hellendahl reached a diagnosis of "sarcoma" in two instances by a histologic examination of a specimen of tissue obtained by probatory puncture He quotes Kronig as the only one preceding him in the use of this method for diagnosing carcinoma of the lung A presumptive diagnosis of carcinoma in the case reported by Peiry was made from the tissue found plugging a large trochar which had been deeply inserted into the lung

The examination of the pleural fluid for cells of the neoplasm has been investigated, particularly by Seecof, who was able to make diagnoses in agreement with the subsequent observations at autopsy in 79 per cent of a series of 38 pleural fluids The diagnosis from isolated cells is much less certain than that from clumps of cells in normal relation to each other

Thus it may be seen that the pathologist can have an important part in establishing the diagnosis of carcinoma of the lung during the life of the patient It is gratifying that statistical studies show that the condition is being diagnosed during the life of the patient much more often than only a few years ago Brunn found that there are at least 28 examples of surgical intervention in the literature, and he cites cases of Sauerbruch in which the patients were living five years and three years after the operations, respectively

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## Notes and News

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**University News, Promotions, Resignations and Appointments**—Ara James Miller, formerly professor of clinical pathology in the University of Nebraska, Omaha, has been appointed professor of pathology and bacteriology in the University of Louisville School of Medicine

Donald C Beaver has been appointed first assistant in pathologic anatomy at the Mayo Clinic, Rochester, Minn

James Henry Dible, professor of pathology and bacteriology in the Welsh National School of Medicine, Cardiff, has been appointed professor of pathology in the University of Liverpool in the place of Warrington York who has been appointed professor of tropical medicine

James S Simmons, Major in the Medical Corps of the U S Army, formerly in charge of the bacteriologic department of the Army Medical School, Washington, D C, has been appointed to the army research board in the Bureau of Science, Manila, P I

George T Caldwell, formerly professor of pathology in Baylor Medical College, Dallas, Texas, has been appointed pathologist of the Charles T Miller Hospital, St Paul, Minn, and a member of the department of pathology in the University of Minnesota

William Thalhimer, formerly pathologist to the Columbia Hospital, Milwaukee, has been appointed director of the Nelson Morris Institute for Medical Research and of the laboratories of Michael Reese Hospital, Chicago, in place of Oscar T Schultz who resigned on account of ill health

Otto Saphir, senior instructor in pathology in Western Reserve University and pathologist to the Cleveland City Hospital, has been appointed pathologist to Michael Reese Hospital, Chicago

**Research Award by The American Society of Clinical Pathologists**—An award will be given annually for work in clinical pathology by a member of this society. The prize will be known as the Ward Burdick Research Award of the American Society of Clinical Pathologists and is to perpetuate the memory of the late Dr Ward Burdick, who fostered the growth of the society as a founder and as its secretary. The award will be in the form of a gold medal for worthy research in any of the fields of clinical pathology. Candidates for the first award must present the reports of their work at least two months prior to the annual meeting to be held in Portland, Ore., July 5, 6 and 8, 1929. Correspondence should be addressed to the American Society of Clinical Pathologists, Metropolitan Building, Denver

**Pathologic Fellowships in Charity Hospital, New Orleans**—The pathologic department of the Charity Hospital, reorganized and placed under the directorship of Dr Rigney D'Aunoy, offers, beginning July 1, 1929, fellowships in pathology. These fellowships extend over a period of two years, and carry with them the rank of assistant resident pathologist and junior resident pathologist of the Charity Hospital. Full maintenance and a stipend of \$900 and \$1,800 yearly is offered fellows. The laboratories are well organized and equipped and provide material for excellent training in the field of laboratory medicine

**The Japanese Journal of Experimental Medicine**—*The Japanese Journal of Experimental Medicine*, edited by Toneji Miyagawa, is a continuation of the Scientific Reports of the Institute for Infectious Diseases of Tokyo Imperial University. The articles are either in the English or in the German language. The first number appears as number 1 of volume 7

# Abstracts from Current Literature

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## Experimental Pathology and Pathologic Physiology

METABOLISM OF TOTAL BASE IN NEPHRITIS G L BOYD, A M COURTNEY and I F MACLACHLAN, Am J Dis Child **36** 16, 1928

There is relatively slight variation in the concentration of the total base of the plasma in different types of nephritis. Such cases as show chronic diffuse or interstitial nephritis, renal acidosis associated with increase in blood phosphates and a positive retention of sodium and chlorine in the body when in conjunction with anasarca tend to be accompanied by a decrease in the concentration of the base of the plasma. This decrease is usually to a low normal, or a slightly lower than normal, figure. It was observed that retention of nitrogen or its absence exerted little effect on the level of the base of the plasma. Neither could a constant relationship be demonstrated between the base of the plasma and the blood dilution, or the base retention of the body, other than the sodium retention.

The total base excreted by a nephritic kidney is usually less than normal, provided diuresis is not occurring or that functional impairment is not present owing to the mild character of the lesion.

Nephritic kidneys which are unable to excrete normal amounts of fixed base show an increase in the excretion of total base and its constituent elements in the feces.

The total base excretion, urine and fecal, in patients with nephritis exceeded that in normal children, despite a comparable intake.

H E LANDT

THE INFLUENCE OF SLEEP ON BASAL METABOLISM OF CHILDREN CHI CHE WANG and R KERN, Am J Dis Child **36** 83, 1928

The authors set forth the fact that there is a definite reduction of heat production in sleeping children. Their data were collected from the study of twelve children. They also conclude that Benedict's standards for basal metabolism of children agree more closely with results obtained for young children during sleep than with those for older children.

H E LANDT

FACTORS INFLUENCING THE EXCRETION OF CALCIUM B HAMILTON and M MORIARTY, Am J Dis Child **36** 450, 1928

The normal variations of the excretion of calcium in the stools of a breast-fed infant were studied, it was found that the excretion of calcium was influenced chiefly by the intake of total fixed base and to a lesser degree by the intake of calcium. As the total fixed base was closely related to the buffer content of the milk (base minus chloride), it seems probable that it was the buffer content of the milk which had this influence on the excretion of calcium in the stools. This view is strengthened by the results in some experiments in which acid and alkali were added to the milk.

The close relationship between calcium in the stools and milk base makes it probable that the former was formed before the latter was absorbed, that is, in the small intestine.

AUTHORS' SUMMARY

THE RESPIRATORY METABOLISM IN INFANCY AND CHILDHOOD J R WILSON, S Z LEVINE and G GOTTSCHALL, Am J Dis Child **36** 470, 1928

The author reports a study of the carbohydrate metabolism of normal and marasmic infants. Some of the infants received subcutaneous injections of insulin before the procedure, an equal number did not. It was found that normal infants

may burn about 0.5 Gm of carbohydrate per kilogram per hour after the ingestion of a large dextrose meal. Marasmic infants burned more than 0.5 Gm per kilogram per hour. They burn less than 0.5 Gm per kilogram per hour on the basis of expected weight for age.

The amount of carbohydrate combustion in an infant at rest following the ingestion of a large dextrose meal depends directly on the amount of metabolic protoplasmic tissue in the infant. The previous administration of insulin had no effect on the amount of carbohydrate burned in normal or marasmic infants. Thus, insulin is not indicated as a therapeutic measure in marasmus.

H E LANDT

THE RÔLE OF HEMOLYSIS IN JAUNDICE OF THE NEW-BORN INFANT J  
MCKENNEY MITCHELL, *Am J Dis Child* 36 486, 1928

The blood serum of the mother contains a substance capable of hemolyzing the red blood cells of her infant in vitro. This substance is demonstrated in 51 per cent of thirty-three infants with jaundice. It is also demonstrated in lower titer in the cord blood of 22 per cent of thirty-three infants with jaundice. All cord serums show an indirect van den Bergh reaction higher than normal. The direct van den Bergh reaction is not present in cord serums. The serums of all infants under 14 days of age show an indirect van den Bergh reaction higher than normal and higher than that of the cord serums. The reading parallels the intensity of jaundice. The direct reaction is not present in simple icterus neonatorum. Increased fragility of the red blood cells is not a factor in the production of jaundice or in cases showing hemolysis by the mother's serum. The time of formation of the blood group in new-born infants does not bear any relation to jaundice.

H E LANDT

THE FLUCTUATION IN BLOOD SUGAR DURING ECLAMPSIA AND ITS RELATION  
TO THE CONVULSIONS P TITUS, P DODDS and E WILLETTTS, *Am J Obst & Gynec* 15 303, 1928

By means of serial readings of the sugar content of the blood, Titus, Dodds and Willetts demonstrated a disturbance in carbohydrate metabolism in eclampsia characterized by a drop in the sugar content of the blood preceding the convulsion. The convulsive seizures occur at levels designated as "absolute," or "relative hypoglycemia," the latter being a sudden definite drop in the sugar content of the blood as compared with previous readings. Following the convulsion there is usually a temporary rise in blood sugar, which is considered the customary response in the liver to muscular activity. There is a tendency to remissions at a lower level so that there is a general trend to a lower sugar content, effecting an eventual exhaustion of the glycogen reserve stored in the liver. The authors conclude that all toxemias of pregnancy are related, and that they are not due to specific toxins of fetal origin. The toxemias are due to a disturbance of maternal metabolism due, primarily, to a deficiency in carbohydrate. The convulsion is comparable to that of hypoglycemia on excessive administration of insulin. The authors therefore propose the injection of dextrose intravenously, 300 cc of a 25 per cent solution at stated intervals.

A J KOBAK

THE TOXICITY OF BLOOD SERUM PROTEINS IN ECLAMPSIA A F LASH and  
W H WELKER, *Am J Obst & Gynec* 15 511, 1928

Blood was obtained from two patients with eclampsia intrapartum and postpartum. After injecting the blood serum proteins fractionated by the method outlined by Hektoen and Welker, the authors concluded that the blood of patients with eclampsia does not show evidence of toxicity in mice, although injected in large doses intraperitoneally.

A J KOBAK



GESTATION IN A MONKEY (MACACUS RHESUS) AND ASSOCIATED PHENOMENA  
C G HARTMAN, Am J Obst & Gynec **15** 534, 1928

For two years, Hartman studied the menstrual cycle and the various matings of the monkey in the case reported. Each cycle was twenty-eight days and lasted less than five days. The vaginal secretion was removed by the "lavage" method, that is, by washing the vagina with from 2 to 3 cc of physiologic sodium chloride solution (the amount varied with the size of the animal). The material thus obtained was placed in a graduated centrifugated tube. After the sediment had settled, it was measured, and then this was again mixed and further diluted and methylene blue added for a cellular study. The leukocyte count dropped to nearly zero in the interval of the cycle. The greatest desquamation was reached in the latter part of the interval, and then a fall to an extremely low cell count occurred at the time for menstruation. The animal, after seven matings, became pregnant only when mated on the interval or twelfth day of the cycle with the leukocyte count at that time showing almost no cells. The pregnancy lasted six lunar months. A slight bleeding occurred on the fourteenth and lasted to the thirty-seventh day of gestation. This was presumed to be from the immature placenta, the so-called "placenta sign" of Long and Evans.

A J KOBAK

ERGOT POISONING POSTPARTUM H LEO MOSKOVITZ, Am J Obst & Gynec  
**15** 549, 1928

From a review of the literature back to 1900 and a study of his own case, Moskovitz shows that ergot poisoning occurs in many cases as an individual idiosyncrasy.

A J KOBAK

THE EFFECTS OF LIGATION OF PANCREATIC DUCTS ON GASTRIC DIGESTION  
S A YESKO, Am J Physiol **86** 483, 1928

In dogs, the effect of ligation of pancreatic ducts showed that with complete absence of pancreatic secretion there was only a slight rise of gastric acidity, the stomach emptied faster, there was increased gastric protein digestion, and increase of blood amylase. Good health was maintained, but there was progressive loss of weight.

H E EGGERS

THE EFFECT OF SUPRARENAL INSUFFICIENCY ON REPRODUCTION AND THE  
OESTROUS CYCLE IN THE ALBINO RAT L C WYMAN, Am J Physiol  
**86** 528, 1928

Double suprarenalectomy in the white rat was found to result in complete or partial inhibition of estrus, the degree of disturbance of ovarian function being correlated with the severity of the insufficiency. The relation appeared to be indirect, working through intermediate factors which were probably metabolic.

H E EGGERS

THE VALUE OF ACTEROL (IRRADIATED CHOLESTEROL) IN THE TREATMENT OF  
THYROPARATHYROIDECTOMIZED DOGS J C BROUGH, Am J Physiol  
**86** 538, 1928

The onset of a violent attack of tetany is prevented in parathyroidectomized dogs by the administration of 0.4 cc of irradiated cholesterol in the presence of milk. Absence of the latter as a source of calcium renders the irradiated cholesterol without effect. Irradiated cholesterol induces more rapid recovery time than does cod liver oil from fifteen to thirty days for the former, and from thirty to forty days for the latter. Apparently, a large supply of vitamin D is effective in many instances to enable the body to use calcium in the condition of parathyroid tetany.

H E EGGERS

LEUKOCYTE CHANGES AFTER ADRENAL REMOVAL R L ZWEMER and C LYONS,  
Am J Physiol 86 545, 1928

In cats which survived adrenalectomy for a long time there was observed a decrease in the number of polymorphonuclear neutrophils and an increase in the small mononuclears. This may be preceded by a postoperative rise in the number of all the white cells associated with trauma and healing. Animals which failed to survive the necessary period showed high total and neutrophil counts—the typical picture of infection. The total count was found to be increased by cold, without effect on the differential count. This increase was apparently related to reaction by the sympathetic nervous system.

H E EGGERS

THE EFFECT OF WITHDRAWAL OF DRINKING WATER ON THE SUSCEPTIBILITY OF RATS TO CERTAIN DRUGS G CRISIER, Am J Physiol 86 552, 1928

When rats were withheld from drinking water for forty-eight hours or more, they showed increased susceptibility to morphia and to magnesium sulphate, and diminished susceptibility to strychnine. It is suggested that in the depression stage of dehydration, animals are more susceptible to depressant drugs, and less sensitive to those which kill by stimulation.

H E EGGLRS

A HORMONE MECHANISM FOR GALL-BLADDER CONTRACTION AND EVACUATION A C IVY and E OLDBERG, Am J Physiol 86 599, 1928

Intravenous injection of an extract of upper duodenal mucosa was found to cause contraction and evacuation of the gallbladder. This extract was free from vasodilator and was without objective toxic effect on unanesthetized dogs. Since cross-circulation experiments showed that the injection of acid into the duodenum caused the appearance of a substance in the blood which resulted in contraction of the gallbladder, the mechanism would appear to be that of hormone action, and for this hormone and the active substance of the intestinal extract, the writers propose the name "cholecystokinin". In addition to dilute acids, the following substances caused contraction of the gallbladder after injection into the duodenum: butter, digested egg yolk, cream and olive oil, and 5 per cent soap solution. Undigested egg yolk, cream or olive oil were without effect. Spontaneous rhythmic contractions of the gallbladder which were observed were increased in amplitude by small doses of "cholecystokinin", larger doses caused their disappearance during the height of the induced contraction, but they reappeared during the subsequent relaxation. If they were not present prior to the injection, they would frequently appear during the late stages of relaxation. During the contraction, the hepatic ducts were observed to be injected with iodized oil 40 per cent, owing, it was believed, to increased tone of the duodenum or of the sphincter of Oddi.

H E EGGERS

CHANGES IN BLOOD SUGAR FOLLOWING INJECTIONS OF PEPTONE IN THE DOG W W BRANDES and J P SIMONDS, Am J Physiol 86 618, 1928

In anesthetized dogs, the injection of peptone was found to cause a peripheral hypoglycemia during the period of low blood pressure, when the liver is engorged and tense. With rise of pressure and decrease in the tenseness of the liver, there is a marked rise in blood sugar. During the period of greatest engorgement of the liver, a marked rise is noted in the sugar of the blood of the hepatic vein, while at the same time that of the peripheral vessels is low. The writers explain this by the obstruction to the free flow of blood through the liver during peptone shock, with the congestion and local stasis causing increased glycogenolysis. This increased production of sugar is retained locally, owing to the small amount of blood leaving the liver. With relaxation of the circulatory obstruction, the peripheral hypoglycemia gives place to a hyperglycemia when the sugar-laden blood leaves the liver.

H E EGGERS

CHANGES IN THE BLOOD RESULTING FROM MECHANICAL OBSTRUCTION OF THE  
HEPATIC VEINS J P SIMONDS and W W BRANDES, *Am J Physiol*  
86 623, 1928

After mechanical constriction of the hepatic vein in dogs, the following blood changes were observed a precipitate fall of blood pressure of from 40 to 60 mm of mercury, with a fairly constant maintenance at this level during the period of constriction of twenty minutes or more, a decided decrease in blood concentration, averaging 11 per cent in six dogs, with a gradual return to normal during the course of about fifteen minutes, a marked decrease of coagulation time during constriction, followed by an increase on release, and a rapid fall of the blood sugar—to an average of 42 per cent in six dogs—with a rapid rise on release

H E EGGERS

RICKETS AND TETANY IN RATS A T SHOHJI and F C BING, *Am J Physiol*  
86 633, 1928

While correction of the defective mineral metabolism of rickets in rats could be accomplished by two essentially opposed methods—by the use of cod liver oil or irradiated food on the one hand, and by the addition of phosphates to the diet on the other—the animals to which the phosphates were administered showed a temporary hyperirritability of the neuromuscular system which was lacking in the others

H E EGGERS

ACTIVITY STUDIES ON CASTRATED MALE AND FEMALE RATS WITH TESTICULAR  
GRAFTS, IN CORRELATION WITH HISTOLOGICAL STUDIES OF THE GRAFTS  
C P RICHTER and G B WISLOCKI, *Am J Physiol* 86 651, 1928

The activity of castrated rats, which is much less than that of normal animals, was found to be greatly increased by testicular grafting, being in general proportional to the state of preservation of the graft In none was the testicular tissue absolutely normal, but the "takes" were much better in the male than in the female animals The increase of activity was much less than that resulting from ovarian transplantation

H E EGGERS

THE BASAL METABOLISM DURING THE OESTROUS CYCLE IN THE RAT M O  
LEE, *Am J Physiol* 86 694, 1928

From a total of 282 basal metabolism determinations made on nine female rats during all stages of the estrual cycle, it was found that in all the animals there was increased heat production during the last ten hours of the diestrus stage, and in the first six hours of the proestrus No change in metabolic rate was found at any other stage The increased heat production during the end of the diestrus is comparable to the slight increase reported in menstruating women No constant changes were found in the respiratory quotients determined in two rats during all stages of the cycle

H E EGGERS

THE CONSTITUTIONAL ENTITY OF EXOPHTHALMIC GOITER AND SO-CALLED  
TOXIC ADENOMA A S WARTHIN, *Ann Int Med* 2 553, 1928

(On February 19, 1924, Warthin addressed a joint meeting of the St Louis Medical Society and the American College of Physicians on the subject which forms the title of this paper Even though the address was not published until December, 1928, the literature of the past five years has contained several references to Graves' constitution (Warthin), for the most part in communications published by those who had learned of this constitutional entity through association with Warthin)

An apparently constantly enlarging clinical syndrome, referable to the thyroid gland, is embraced under the general conception of hyperthyroidism and variously designated as toxic goiter, toxic thyroid and toxic adenoma. Clinicians have endeavored to distinguish this form of disease of the thyroid gland from typical or true exophthalmic goiter. Warthin has attempted to correlate the various clinical conceptions of these diseases with the pathologic histology of the thyroid gland. The abundance of material which has poured into pathologic laboratories during recent years should aid in clarifying the divergent views on the pathology of the thyroid gland.

To the original triad of goiter, tachycardia and exophthalmos, recognized vaguely by Parry (1825) and more accurately by Graves (1835) and von Basedow (1840), has been added symptom after symptom until, at the present time, it has become practically impossible, in many cases, to distinguish between what some authors regard as exophthalmic goiter and what others call by such names as toxic adenoma and toxic goiter.

The present day conception of exophthalmic goiter is that of an extremely variable and broad syndrome. Considered analytically, this syndrome presents a clinical picture of a well defined type of person, a distinct pathologic constitution. American writers on goiter have not grasped this fact, but in Germany and Italy, various investigators are beginning to speak of the hyperthyroid constitution. Warthin prefers to term it Graves' constitution in the absence of any positive proof that thyroid hypersecretion is the underlying etiologic factor.

The person with the Graves constitution usually has a youthful build with a slender skeleton, and is usually underweight. The facies has a bright-eyed, quick-reactioned appearance. Tremor of the muscles is usually present. The skin is warm, moist, delicate and translucent, often with a tendency to excessive pigmentation when exposed to light. Vitiligo is not rare. Hyperhidrosis and dermatographia are common. The neck is usually rounded and full, the cervical lymph nodes are enlarged. The thyroid gland is usually, though not always, enlarged. All conditions of the eyes exist, from the vivacious, widely opened state to frank exophthalmos. There is marked cardiac excitability, usually with tachycardia. The pulse is rapid and full and frequently irregular. Vasomotor instability, with flushing, sweating and circumscribed edemas is commonly seen. Instability of the central nervous system manifests itself in increased sensibilities and emotional responses, quickness of perception and reaction, unrest and haste, anxiety, insomnia, flights of ideas and even hysteria and psychosis. Usually, however, the mental powers are well developed and remain well preserved. The marked irritability of the sympathetic nervous system is a predominant characteristic of the condition. The basal metabolism is definitely elevated. The appetite is abnormal, but despite overeating, the person remains thin or loses weight. There is frequently a lowered tolerance for carbohydrates with the development of hyperglycemia. Allergic reactions are common. A mild anemia usually exists, with a relative lymphocytosis. Psychic frequently exceeds physical sexual excitability. Impotency is common in the male, menstrual disturbance in the female. There is diminished tolerance for thyroid preparations, iodine and epinephrine. The most striking features of Graves' constitution are expressed in juvenile morphology and rapid functional reactions. Obviously, these constitutional features will appear in varying degrees of intensity and in varying combinations in different persons.

The clinical diagnosis of hyperthyroidism is frequently being made from the presence of one or two of the symptoms which may belong to the constitutional picture just described, but which may not be associated with any disturbance of thyroid function. Many normal thyroid glands, simple goiters and adenomas are called hyperfunctioning or toxic and are ligulized and resected, only to show that histologic examination does not confirm the clinical diagnosis.

Numerous instances of iodism are resulting from the widespread use of preparations of iodine. Symptoms of palpitation, excitable pulse and nervousness appear, resection is ultimately performed, and the pathologist finds nothing but thin, watery colloid and follicular atrophy, he can do no more than return a diagnosis of "hyperiodism."

If the pathologist accepts the histologic criteria used commonly for the diagnosis of hyperthyroidism or toxic adenoma, namely, epithelial hypertrophy and hyperplasia, he falls at once into difficulties, for many of the thyroid glands sent to him will present no such evidence. If the classic clinical signs of exophthalmic goiter are present, the pathologist expects to find diffuse parenchymatous hyperplasia and metaplasia with total absence, or marked decrease, of colloid. When these are found, the pathologist unhesitatingly makes a diagnosis of exophthalmic goiter. If the parenchymatous hyperplasia is focal, many pathologists will regard it as evidence of early, moderate or incomplete exophthalmic goiter. The greatest difficulty presents itself in those cases in which, with precisely the same symptomatology, no epithelial hyperplasia or hypertrophy can be found. The pathologist is further perplexed by the fact that epithelial hypertrophy may be found in the thyroid glands of persons who were not suspected clinically of thyroid hyperfunction or dysfunction. There is no positive knowledge as to the exact relationship between the histologic appearances of the thyroid epithelium and its functional activity. As far as thyroid epithelium is concerned, therefore, there are no histologic criteria that give a pathologic unity to all the clinical forms of thyroid hyperfunction or dysfunction.

Warthin considers that the most interesting and striking feature of the thyroid gland in exophthalmic goiter is the constant presence of hyperplastic lymph nodules with large germinal centers showing the characteristic lymphoid exhaustion of the thymicolymphatic constitution. American authors have attached no significance to this constant observation. On the other hand, a large number of European authors have noted the constant presence of an enlarged thymus in cases of exophthalmic goiter. A few mention the presence of hyperplastic lymph nodes within the thyroid itself. Chvostek, however, is almost the only author who regarded the general picture of exophthalmic goiter as indicating the thymicolymphatic constitution. No one has observed the occurrence of the same pathologic constitution in the so-called toxic adenoma.

Warthin's experience has been vastly different. In the first sections of exophthalmic goiter which he studied, he was struck by the presence of hyperplastic lymphoid tissue with exhaustion of the germ centers, resembling that of the thymicolymphatic constitution. Warthin recently restudied 976 resected thyroid glands submitted to him from 1900 to 1923, the autopsy material of thirty post-operative deaths in cases of exophthalmic goiter and in five deaths in acute cases of this disease without operation, and the thyroid glands at 1,000 autopsies in which the thyroid had been examined by the routine procedure. In 150 of the autopsies, a pathologic diagnosis of thymicolymphatic constitution had been made.

Among the 976 resected thyroid glands were 50 which showed diffuse epithelial hypertrophy and hyperplasia with lymphoid hyperplasia, 45 showed nodular colloid goiter with focal epithelial hypertrophy and lymphoid hyperplasia, 58 were true adenomatous colloid goiters with focal epithelial hypertrophy and lymphoid hyperplasia, 92 were true adenomatous colloid goiters with lymph hyperplasia, but without epithelial hypertrophy.

The clinical diagnosis of exophthalmic goiter, hyperthyroidism, toxic goiter or toxic adenoma was made in the case of adenomatous, nodular and colloid goiters showing lymphoid hyperplasia, either with or without epithelial hypertrophy. As far as could be learned, other signs of Graves' (thymicolymphatic) constitution were present in the majority of these cases.

In the 1,000 autopsies studied, 94 cases showed lymphoid hyperplasia of the thyroid gland. In all these cases, as well as in the thirty-five autopsy cases of exophthalmic goiter, with diffuse epithelial and lymphoid hyperplasia, there was found associated the general picture of thymicolymphatic constitution: hyperplastic or persistent thymus, general enlargement of the lymph nodes and spleen, hypoplasia of the suprarenal glands, heart and aorta with other morphologic stigmas.

Warthin states that it is apparent from these studies that the constitutional defect of the thymicolymphatic (Graves') constitution underlies every case of exophthalmic goiter and so-called toxic adenoma. An adenoma of the thyroid

gland, aside from its size and mechanical effects, is clinically important as far as so-called toxic symptoms are concerned only when it is associated with the thymico-lymphatic constitution. Exophthalmic goiter and "toxic adenoma," therefore, possess the same pathologic constitutional entity. Not all cases of thymico-lymphatic constitution will present the Graves syndrome, but all cases with the latter will possess the essential morphologic stigmas of this constitution. Exophthalmic goiter and toxic adenoma are pathologic reactions potentially predetermined in the person at birth by virtue of his constitutional anomaly. Only those possessing this constitutional anomaly will develop so-called hyperthyroid or thyreotoxic symptoms. The potentiality, however, may remain latent or quiescent during all or a large part of the life of a person possessing the constitutional background.

WALTER M. SIMPSON

ENDMIC GOITER IN RABBITS ALAN M. CHLSON, THOMAS A. CLAWSON and  
BRUCE WEBSTER, Bull. Johns Hopkins Hosp. 43: 261, 278 and 291, 1928

Marked spontaneous enlargement of the thyroid gland was observed in a series of rabbits kept under identical conditions in the laboratory. The average weight of the thyroid was 293 Gm., the maximum was 43 Gm. The glands showed increased vascularity, with hyperplasia, but without increase in colloid. Enlargement of the suprarenal glands was also present in some of these animals. The time during which the rabbits remained in the laboratory seemed to be a factor in the development of the goiters. Although most of them were used in the study of syphilis, it was possible to exclude this disease as an essential factor in the condition.

The heat production of normal rabbits and those with goiter was studied by means of Marine's modification of Haldane's apparatus for measuring the respiratory exchange in rabbits. In normal animals, the average metabolic rate was 264 calories per kilogram per hour, while in those with palpable goiters it was 22 calories, a decrease of 166 per cent. The decrease paralleled, to some extent, the degree of enlargement of the thyroid. Study of individual animals showed gradual depression of the metabolic rate, with growth of the goiter in the majority. Certain animals, which died without obvious cause but with extreme loss of weight, showed an average increase of 20 per cent in their metabolic rate before death.

Administration of iodine in the form of a compound solution of iodine, 0.06 cc daily, caused a temporary lowering of the metabolic rate in six normal rabbits, followed by a gradual return to normal. Diffuse out-pouring of colloid was produced, with flattening of the alveolar epithelium, and preponderance of the colloid cells. In rabbits with goiter, on the other hand, there was an immediate increase in the activity of the animals, a marked increase in the metabolic rate, rapid emaciation and death, in most instances. The average increase was 98 per cent, the severity of the reaction being proportional to the degree of hyperplasia in the gland. Examination of the thyroid glands revealed involution of the hyperplastic glands and lowering of the alveolar epithelium, with areas resembling colloid adenomas. It would appear that, as soon as the deficiency of iodine was supplied, the gland was able to pour an excess of thyroid secretion into the blood. These experiments suggest that large doses of iodine may be dangerous to persons with simple goiters of the iodine deficiency type.

B. R. LOVETT

ON THE PATHOGENESIS OF THE ARGYLL-ROBERTSON PHENOMENON SVEN  
INGVAR, Bull. Johns Hopkins Hosp. 43: 363, 1928

For the evolutionary reasons developed in the article, one must look for the pupillomotor pathways on the surface of the diencephalon. It is known that they take a surface route from the posterior part of the optic tract to the anterior commissure in front of the anterior quadrigeminal bodies. As the metasyphilitic and syphilitic meningitic processes produce successively developing marginal degenerations of the optic pathways, as also of the diencephalic parts on the whole, the pupillomotor pathways must be injured at an early stage. In fact, all the char-

acteristic features of the Argyll-Robertson pupil are to be explained in this manner. The reflex immobility of the pupil is to be considered simply as a meningitic symptom. In this way only does the Argyll-Robertson pupil acquire significance clinically. The disturbed pupillary reaction to light reflects the processes within the basal subarachnoid spaces along the optic pathways. It appears to be a sensitive indicator of these processes when the disturbance occurs in the early stages. Such an indicator is certainly also the isolated ptosis in metasyphilitic processes. In the same way, one attains an understanding of the pupillary disturbances after traumatic lesions. As all the evidence indicates that only such morbid processes as manifest themselves in producing marginal destructions within the basal subarachnoid spaces of the brain are able to cause the Argyll-Robertson pupil, it is understood that the metasyphilitic and syphilitic diseases hold a monopoly among the causes of this valuable clinical symptom.

AUTHOR'S SUMMARY

THE EFFECT OF SODIUM CHLORIDES ON THE CHEMICAL CHANGES IN THE BLOOD OF THE DOG AFTER OBSTRUCTION OF THE CARDIAC END OF THE STOMACH  
RUSSELL L. HADEN and THOMAS G. ORR, *J. Exper. Med.* **48** 627, 1928

A study is reported of the effect of different methods of treatment on the toxemia of cardiac obstruction. The average duration of life of untreated dogs is three days. Three dogs treated with 1 per cent salt solution subcutaneously lived thirty-two, thirty-six and forty-five days, respectively, without developing a toxemia. Two per cent dextrose, similarly given, does not alter the course of the toxemia. Concentrated salt solution in small quantities, given directly into the jejunum, prevents the marked rise in nonprotein nitrogen but does not materially prolong life. Release of the obstruction does not change the course of the toxemia in untreated animals. The subcutaneous injection of 1 per cent sodium chloride solution after release of the obstruction causes a rapid return of the blood to normal and allows the animal to recover. A similar amount of fluid given as 2 per cent dextrose does not alter the course of the toxemia after release of the obstruction.

AUTHORS' SUMMARY

THE BLOOD CHLORIDES IN PROTEOSE INTOXICATION. RUSSELL L. HADEN and THOMAS G. ORR, *J. Exper. Med.* **48** 639, 1928

Dogs injected with proteose recovered from the intestinal contents of animals with obstruction at different levels show no significant changes in the blood chlorides even with a fatal intoxication. After the intravenous injection of lethal and sublethal doses of Witte's peptone, there is little change in the chlorides. Autolyzing liver in the abdominal cavity produces no change in the blood chlorides, even with a great increase in the urea and nonprotein nitrogen. Proteose intoxication is probably not a factor in the characteristic fall in chlorides seen after intestinal and pyloric obstruction.

AUTHORS' SUMMARY

ON THE PERIOD OF HUMAN GESTATION. W. A. JOLLY, *J. Obst. & Gynec. Brit. Emp.* **35** 258, 1928

Two factors determine the length of gestation, they are dependent on the rhythmic endocrine influence, and the irritability and tolerance of the uterus to its distention in the last months of pregnancy. The period of human gestation is related to the length of the menstrual cycle. The physiologic period extends over eleven cycles instead of the current accepted ten cyclic periods. This is reckoned from the middle day of the last cycle, i. e., when the menstrual cycles are short and regular, such as twenty-four days, the pregnancy, counted from the last menstrual flow, lasts 264 days, or eleven cycles. When the period of gestation is figured from the time of ovulation, which is usually about the fourteenth day, the length of gestation would amount to 252 days, or ten and one-half cycles.

A. J. KOBAC

THE RESORPTION OF THE BILIARY ACIDS IN THE NORMAL AND INFLAMED GALL  
BLADDER F ROSENTHAL and H LICHT, *Klin Wchnschr* 7 1952, 1928

Severe inflammations of the gallbladder markedly increase the absorption of biliary acids

E F HIRSCH

HYPOLYCEMIA IN ADDISON'S DISEASE W WADI, *Klin Wchnschr* 7 2107, 1928

The report stresses the hypoglycemia which appeared in the late stages of the disease in his patient, with coma and muscle twitchings Dextrose temporarily relieved these symptoms

E F HIRSCH

THE EFFECT OF TRAINING ON THE WORK CURVE OF BLOOD SUGAR A HOF-  
MANN, *Klin Wchnschr* 7.2043, 1928

As Burger already supposed, the hyperglycemia with work diminishes with training, and finally disappears Further, the hypoglycemia decreases so that finally, in a well trained person, the sugar curve is practically a straight line

AUTHOR'S SUMMARY

LIPID METABOLISM IN FASTING ANIMALS H WENDT, *Klin Wchnschr* 7 2183, 1928

In fasting dogs, the phospholipins and cholesterol increase in amount in the peripheral blood during the first few days and gradually decrease later to sub-normal values The free cholesterol and the esterified cholesterol participate about equally in the initial increase and subsequent diminution The increase of phospholipin and cholesterol ester noted in normal animals after triolein feeding is much more accentuated in the fasting dog Correlation is sought by the assumption that fat is destroyed more quickly than lecithin or the cholesterol esters

AUTHOR'S SUMMARY

### Pathologic Anatomy

MYOCARDITIS B J CLAWSON, *Am Heart J* 4 1 (Oct) 1928

Myocarditis, acute or chronic, arranged diffusely or in localized areas as Aschoff nodules or abscesses, is a common condition in the myocardium in acute and recurrent rheumatic endocarditis, in subacute bacterial endocarditis and in old valve defects The periarterial scars appear to be the result of a previous bacterial infection and are frequently found in the myocardium in cases of subacute bacterial endocarditis and old valve defects Proliferative or exudative inflammation is rare in the myocardium in cases of syphilitic aortitis Scars resulting from atrophy of muscle with replacement by connective tissue following a narrowing of coronary arteries seldom occur except in the myocardium in cases of hypertension and coronary sclerosis The extent of myocardial injury as shown by anatomic changes rarely appears to be sufficient to bring about cardiac failure The conditions usually diagnosed acute or chronic myocarditis cannot be demonstrated clinically to be inflammatory processes and in most cases anatomic injuries are not seen So-called myocarditis is usually a condition of the myocardium, probably fatigue, which is not manifested anatomically

AUTHOR'S SUMMARY

ABNORMALLY LONG PAPILLARY MUSCLES OF THE HUMAN HEART WALLACE  
M YATER, *Am Heart J* 4 72 (Oct) 1928

This type of anomaly is undoubtedly congenital Early in the development of the atrioventricular valves, muscular tissue from the myocardium invades the endocardial tissue of the cusps and replaces it The muscular tissue of the cusps



becomes closely blended with the subjacent musculature of the walls of the ventricles. This stage in the development of the cusps is soon followed by replacement of the muscular tissue by collagenous connective tissue, the process evidently taking place mainly from above downward. The subjacent trabeculate musculature also is replaced by collagenous connective tissue. The fibrous cords so developed are the chordae tendineae. Muscular tissue persists at the parietal ends of the cords and forms the papillary muscles.

In cases such as those just described, the replacement by collagenous connective tissue ceases too soon and is imperfect, muscular tissue is left in place of chordae tendineae. The only other explanation would be that localized endocarditis had produced thickening and retraction of the chordae tendineae, causing the cusp of the valve and the papillary muscle to be drawn together. All the facts, however, are opposed to this conception and point rather to the developmental origin of the condition. The instances of this anomaly previously reported and those described in this paper have not appeared to possess any clinical significance. In case 2 of this series it seemed that the condition might have increased the insufficiency of a dilated mitral ring had such been present, but the mitral orifice was apparently not very incompetent.

## AUTHOR'S SUMMARY

THE RELATION OF THE WEIGHT OF THE HEART TO THE WEIGHT OF THE BODY  
AND OF THE WEIGHT OF THE HEART TO AGE HARRY L. SMITH, *Am Heart J* 4 79, 1928

The average weight of the adult male heart is 294 Gm, that of the adult female heart is 250 Gm. There is a definite correlation between the weight of the heart and weight of the body. The ratio is 0.43 per cent for males, and 0.40 per cent for females, it is slightly higher in thin persons and lower in obese persons. This coefficient is not accurate for body weights of less than 45 Kg and more than 94.5 Kg. The weight of the heart may be calculated from the weight of the body, with an error varying from 8 to 10 per cent. The weight of the heart does not increase with age, irrespective of the weight of the body, it increases, however, with increase in the weight of the body.

## AUTHOR'S SUMMARY

THE LONGITUDINAL SMOOTH MUSCLE OF THE CENTRAL VEIN OF THE SUPRARENAL GLAND EARL FLETCHER HENDERSON, *Anat Rec* 36 69 (July) 1927

The musculature of the medullary veins of the suprarenal gland occurs as heavy longitudinal bundles in the wall of the central vein and its tributaries. No circular bundles are found. In smaller veins the bundles are usually single and rounded, and often appear to project far into the lumen of the vessel. In larger veins there are two or more bundles in the wall. Increasing in size and number, they encroach on one another, lose their rounded contour and become more flattened and more uniformly distributed. Before emerging from the gland, the main trunk of the central vein is a thick-walled vessel consisting of an endothelial intima, a strong muscular coat of longitudinal smooth muscle fibers arranged uniformly about its circumference, and a connective-tissue adventitia.

To determine the course of these bundles, segments of the central vein were reconstructed in wax. As small veins with only one longitudinal muscle bundle unite, muscles on adjacent sides of the vessels fuse in the angle of anastomosis. When a larger vein approaches a point of anastomosis with a similar one, the longitudinal fibers usually arrange themselves in two main masses, one on the side nearest the approaching vessel, the other on the opposite side. When the vessels unite, bundles on adjacent sides fuse in the angle, those on opposite sides continue along the outer walls of the vessels.

Because of this arrangement, contraction of the musculature results in dilatation of the central vein. Apparently this muscle regulates the outflow of blood and epinephrine through the suprarenal vein into the general circulation.

## AUTHOR'S SUMMARY

THE SIGNIFICANCE OF THE CONCENTRIC CORPUSCLES OF HASSALL HARVEY  
 ERNEST JORDAN and GUY WINSTON HORSLEY, Anat Rec 35 279 (June)  
 1927

Histologic evidence is presented for an interpretation of the concentric corpuscles of the thymus in terms of foci of occlusion of capillaries and precapillary arterioles following endothelial-cell hypertrophy in involution. Structures closely resembling Hassall's corpuscles of the thymus, and clearly representing segments of precapillary arterioles in which the lumen has become obliterated through hypertrophy of the endothelium, are described in the case of certain involuting lymph nodes of the rabbit.

AUTHORS' SUMMARY

AIR IN THE CORONARY ARTERIES GEORGE J. RUASTINAT and E. R. LE COUNT,  
 J. A. M. A. 91 1776 (Dec. 8) 1928

Experience with some forms of death of human beings and with occurrences in which the approach of death has been close, and the results of experimental air embolism of the pulmonary veins and systemic arteries in guinea-pigs indicate that postmortem examinations of human bodies should now and then be done under water or with other appropriate measures for demonstrating the presence or absence of air in the systemic arteries, especially in those which supply the heart muscle.

In conditions in which air embolism is possible, particularly embolism of the pulmonary veins, the patient should be promptly examined for peculiar churning murmurs of the heart whenever unexpected syncope is encountered and such examinations are feasible.

AUTHORS' SUMMARY

MUSSEL POISONING K. F. MEYER, H. HOMER and P. SCHOEHLER, J. Prev.  
 Med. 2 365, 1928

In a review of several phases of mussel poisoning in California in 1927, four fatal cases are reported. The only lesions found were small hemorrhages in the fundus of the stomach and the first portion of the duodenum.

ADDISON'S DISEASE WITH ATROPHY OF SUPRARENAL CORTEX O. BRENNER,  
 Quart. J. Med. 22 121 (Oct.) 1928

Five cases of Addison's disease are described. In four of them there was a peculiar and characteristic lesion of the cortex, with destruction of most of it. The medulla was little or not at all injured. In the fifth case no suprarenal glands were found. It is suggested that this may represent the end stage of the process illustrated by the other four cases. It is suggested that the process is a necrosis of cortical cells caused by some unknown toxin which has a special affinity for them. This is followed by focal regeneration, with the production of hyperplastic islands of hypertrophied cells, which are then attacked by the same process. The few cortical cells left after the primary injury are probably overworked, possibly causing part of the subsequent degeneration. In many cases of Addison's disease due to suprarenal atrophy or tuberculosis, other endocrine glands are also diseased. In one case the lesion of the thyroid was almost as marked as that of the suprarenal glands, though there were no symptoms of disease of the thyroid. In another case there were mild symptomless lesions of the thyroid and testis. In another case there were symptoms and pathologic changes of exophthalmic goiter as well as of Addison's disease. In the other two cases the other endocrine glands were not examined. The pathologic evidence as to the relative importance of the cortex and medulla is reviewed. It is shown that the symptoms of Addison's disease occur only when most of the cortex is destroyed, and that they occur then even if the medulla and the chromaffin system are normal. On the other hand, the chromaffin system may be absent, and if the cortex is normal there are no symptoms of Addison's disease. The inference is drawn that the symptoms are due to disease of the suprarenal cortex and not to disease of the medulla or of the chromaffin system as a whole.

CONGENITAL STRUCTURAL ANOMALIES OF THE PULMONARY ARTERY A COSTA,  
Arch di pat et clin med 7 329 (Sept) 1928

This study is based on histologic and micrometric examinations of pulmonary arteries (210 cases) in various decades of life and of both sexes. In each instance, the micrometric measurements of the single layers of the arterial wall and the histo-analysis were made in the lower third of the artery. Under normal conditions, the thickness of the media in children varies between 0.35 and 0.5 mm, in the adolescent periods of life it reaches a thickness of from 0.6 to 0.650 mm, and in advancing age it measures between 0.7 and 0.85 mm. While the intimal layer is extremely thin (0.01 mm) in the first years of life, it presents in adolescence a gradual enlargement, showing a thickness of from 0.015 to 0.02 mm and in later decades, 0.03 mm. This progressive enlargement of the media is due to an increase in the density of the circulatory distributed elastic lamellae and to a further development of the muscle tissue. The gradual thickening of the intima occurs on account of the increasing density of the internal elastic membrane and the formation of a delicate subendothelial layer of connective tissue.

The structural malformations found were mainly of hypoplastic nature. Three definite types were observed. 1 Muscular hypoplasia affects the artery diffusely and is characterized by muscle tissue that is little developed or totally absent. The elastic apparatus, as well as the interstitial connective tissues, often appear hyperplastic. However, the muscular hypoplasia rarely occurs, without a concomitant hyperplasia of these two tissues. 2 In another type of musculo-elastic hypoplasia, not only are the muscular elements scarce, but also the structurally important, circularly-running elastic lamellae are extraordinarily thin. The interstitial connective tissue usually exhibits a diffuse hyperplasia. 3 The elastic hypoplasia is characterized by greatly hypoplastic elastic apparatus, while the muscular tissue reaches an otherwise moderate development. In hypoplastic conditions of the first and second types, the media may show a nearly normal thickness (0.75 mm in persons from 30 to 40 years of age) due to hyperplastic processes of other tissues. In the second type, however, the media never achieves its normal size and the pulmonary artery then greatly resembles its early (from 1 to 5 years of age) forms during extrauterine development. The intima does not exhibit any structural abnormalities in the aforementioned hypoplastic conditions of the media, except that the internal elastic membrane participates, more or less, in hyperplastic or hypoplastic processes of the media layer. These investigations do not confirm the observations of Orlansky in regard to hypoplasia of the cerebral arteries (These de Geneve, 1919).

In 14 per cent of all the cases examined post mortem, such structural anomalies of the pulmonary artery were observed. One could not establish any correlation between the described anomalies of the pulmonary wall and the development of atherosclerosis. In 90 per cent of the cases investigated there was a parallelism between the hypoplasia of the aorta and hypoplastic conditions of the pulmonary artery, in 16 per cent of the cases with the latter condition a chronic pulmonary tuberculosis was present.

E. L. MILOSLAVICH

THE THYROID GLAND IN GOITROUS AND GOITER-FREE REGIONS H. MAY,  
Arch f klin Chir 149 501, 1928

May studied the size of the acini and the extension of epithelial proliferation in nongoitrous thyroid glands from different regions. He found a larger histologic development of the thyroid glands of the goitrous region compared with the glands of goiter-free regions. This difference appears striking in a comparison of the enlargement of the thyroid glands at puberty. In the female the histologic development at puberty is always more extensive than in the male. The thyroid gland of the male becomes noticeably enlarged after the age of 60, a new proliferation which does not seem to occur in the female.

C. A. HELLWIG

TOLYLENEDIAMINICERUS II EITLI, Beitr z path Anat u z allg Path  
79 700, 1928

The work emphasizes the causation of icterus by tolylenediamine as due to capillary thrombosis of the bile-ducts rather than to damage to liver-cells. Subcutaneous injection of tolylenediamine causes a bilirubinemia with the appearance shortly of both bile pigment and bile salts in the urine. Biliary thrombi fill the biliary capillaries but the liver cells are scarcely altered.

JESSE LOUIS SERBY

TOLYLENEDIAMINICERUS D YLISA, Beitr z path Anat u z allg Path  
79 712, 1928

Tolylenediamine gives a brownish discoloration to the blood for about twelve hours after injection, thus preventing the study of bilirubin by the van den Bergh test during that time. Dextrose administered at intervals of two hours does not delay the appearance of the icterus. The ligation of the thoracic duct in a normal animal does not give any large collection of bilirubin in the duct, whereas in an animal given tolylenediamine the ligated thoracic duct contains twice and three times the amount of bilirubin that is in the blood. The icterus caused by tolylenediamine results from a resorption of bile as well from hepatogenous and hematogenous changes.

JESSE LOUIS SERBY

CONTRIBUTION TO THE KNOWLEDGE OF PERIARTERITIS NODOSA S. NAUHEIM,  
Frankfurt Ztschr f Path 36 32, 1928

A case of periarteritis nodosa in which only the smallest arteries were affected and which was therefore recognized only by microscopic examination is described. Associated with the arterial lesion was malignant sclerosis of the kidney and an old pulmonary endocarditis. This association seems to support the conclusion of Fehr that a vascular poison is concerned in the production of the malignant sclerosis and to favor the idea that the periarteritis is not the result of a specific agent.

JEAN OLIVER

ANEURYSMA DISSEANS ON A SYPHILITIC BASIS ADALBERT LOESCHKE, Frank-  
furt Ztschr f Path 36 56, 1928

Although the etiology of dissecting aneurysms is not yet entirely clear, the author believes that in all cases a preliminary damage of the arterial wall must be assumed. The newly formed channel of the aneurysm can take on the function of the original vessel and can even undergo the same pathologic process that are observed in arteries. Ordinarily a syphilitic aortitis does not favor the development of dissecting aneurysms, but a case is described in which they occurred due to a nodular gumma in the aortic wall. The author believes that the origin of the other cases of syphilitic dissecting aneurysm reported in the literature are to be explained in a similar way.

JEAN OLIVER

TWO RARE OBSERVATIONS IN OXYURIS INFESTATION OF MAN HELMUTH  
NATHAN, Frankfurt Ztschr f Path 36 82, 1928

In a case of perirectal abscess oxyuris were found surrounded by a granulation tissue in which there were many foreign body giant cells. In another case of cirrhosis, ova and embryos of oxyuris were found in cystlike structures in the spleen. The location of these was explained by a retrograde passage from the portal blood stream, this being favored by the portal stasis which the cirrhosis had caused.

JEAN OLIVER

THE HISTOLOGIC CHANGES OF THE THYMUS GLAND IN CHILDREN WITH SCARLET  
FEVER P. W. SSIPOWSKY, Frankfurt Ztschr f Path 36 123, 1928

The weight of the thymus gland was found to be less than normal in a series of twenty-nine children who had had scarlet fever. This loss of weight was due

to a disappearance of the lymphocytes, an effect of the toxin. The lobules of the organ thus lose their typical differentiation. The medullar and cortical portion of the thymus gland both show a predominance of the reticulo-epithelial structure. There is even a proliferation of the latter formations, so that macrophage-like cells are found which are filled with fat. The picture of these changes is therefore similar to those described for other acute infectious diseases such as dysentery or diphtheria.

JEAN OLIVER

COMPARATIVE INVESTIGATIONS OF THYROID GLANDS IN PERSONS BETWEEN THE AGES OF 25 AND 50. HANS SCHAEER, Frankfurt Ztschr f Path **36** 249, 1928

For the accumulation of the normal data concerning the thyroid gland in middle Europe, only the north German coast (Kiel and Königsberg) can be considered. In all other regions endemic goiter is more or less prevalent. The weight of the organ is of little significance. Variations in the size of follicles are more important as indication of abnormality. The condition of thyroid glands in Kiel is contrasted with that of thyroid glands in Bern. Curves constructed on the age and average dimensions of the follicles in the two regions showed marked difference, nuclear changes, proliferation and desquamation of the epithelium, and other changes in the two regions are noted.

JEAN OLIVER

### Pathologic Chemistry and Physics

STUDIES ON PERMEABILITY OF MEMBRANES. A. A. WEECH and L. J. MICHAELIS, Gen Physiol **12** 55 and 221, 1928

In a study of the relative rates of passage through dried collodion membranes of various nonelectrolytes, it was found that acetone and urea pass through the membrane much more rapidly than glycerin, and glycerin in turn much faster than dextrose. The rate was found to vary directly with the difference in concentration on the two sides. The presence of glycerin on both sides of the membrane did not interfere with the passage of acetone. Experiments are described which suggest that with large molecules, as those of dextrose, there is a gradual clogging of the pores of the membrane until a stationary gradient is reached. The experimental data are explained on the conception of the membrane as a sieve with pores. The different diffusion rates are accordingly regarded as due to differences in molecular size, smaller molecules having a far greater pore area available for their passage than do the larger ones. It is estimated that 98 per cent of the pore area available for diffusion of acetone is unavailable for glycerin, and for dextrose only 0.3 per cent of this area is available.

A mensurative study was made of dried collodion membrane, including determinations of thickness and of relative proportions of collodion volume and pore volume. Evidence is produced that smaller molecules utilize a much larger percentage of total pore area for diffusion than do larger molecules.

H. E. EGGERS

THE PROTEIN CONTENT OF THE CEREBROSPINAL FLUID IN MYXEDEMA. W. O. THOMPSON, P. K. THOMPSON, E. SILVEUS and M. E. DAILEY, J Clin Investigation **6** 251, 1928

In seventeen cases of myxedema, the protein concentration of the spinal fluid was found to be high. It usually dropped to normal limits with the administration of thyroid extract. A differential point is thus given in the rare case in which myxedema may be confused with tumor of the brain or chronic nephritis.

H. R. FISHBACK

THE PLASMA IN SEVERE DIABETIC ACIDOSIS A F HARTMANN and D C DARROW, J Clin Investigation 6 257, 1928

The composition of the blood plasma was studied in six cases of severe diabetic acidosis and also during the period of recovery. It was shown that marked concentration of the plasma occurred with but slight diminution of total base. The decrease of bicarbonate and chloride was relatively greater than the increase of ketone acid and protein. Treatment with water and insulin, with or without carbohydrate, restored the bicarbonate and  $p_H$  relatively slowly at first, and the addition of salt solution aided but little in bicarbonate recovery. The combination of sodium bicarbonate with water, insulin, carbohydrate and sodium chloride provided a rapid and complete relief from acidosis.

H R FISHBACK

THE  $p_H$  OF THE URINE UNDER VITAL CONDITIONS A BECK and H J LAUBER, Klin Wchnschr 7 2241, 1928

$p_H$  determinations of the urine with indicators is often without regard for the carbon dioxide tension. A shift in the  $p_H$  to a more alkaline (or less acid) reaction occurs promptly when carbon dioxide escapes, greater with alkaline urines than acid. Temperature variations also influence markedly the carbon dioxide tension and consequently the  $p_H$ .

EDWIN F HIRSCH

### Microbiology and Parasitology

CYTOLYSIS IN THE CEREBROSPINAL FLUID IN ACUTE POLIOMYELITIS G LYON, Am J Dis Child 36 40, 1928

Cytolysis has been observed in the early pleocytoses of acute poliomyelitis, which is more active toward the multilobed elements than toward the mononuclear elements.

Proof is given of the advisability of making cell counts of the spinal fluid immediately after lumbar puncture in all cases in which there may be a possibility of poliomyelitis.

A pleocytosis consisting of 50 per cent or more of multilobed cells, occurring in a clear fluid, is suggestive of acute poliomyelitic infection. When in the course of from twenty-four to thirty-six hours, the lumbar puncture is repeated and there is a fall in the total cell count with a shifting of the differential count to a mononucleosis of 90 per cent or more, one may be certain that the condition is one of poliomyelitic infection. This cellular response is pathognomonic, as it has not been observed in the spinal fluid in other conditions.

AUTHOR'S SUMMARY

INFECTION OF THE CONJUNCTIVA AND CORNEA OF GUINEA-PIGS FOLLOWING THE APPLICATION OF VIRULENT DIPHTEHRIA BACILLI MARGARET BEATTIE, Am J Hyg 8 502, 1928

The application of diphtheria bacilli to the previously irritated eyes of guinea-pigs for the purpose of detecting the immunity of animals immunized against diphtheria is not reliable, since 50 per cent of normal animals tested were not infected.

PEARL ZEEK

INFECTION WITH STRONGYLOIDES STERCORARIIS J H SANDGROUND, Am J Hyg 8 507, 1928

Dogs and cats of all ages were successfully infected with *Strongyloides stercoralis* secured from a human patient. The animals showed certain decided differences in susceptibility to the disease and to its duration. The infections disappeared spontaneously and were followed by the acquired immunity which, in dogs, lasted for more than six months. The development of immunity was thought to be

intimately associated with the relationship that existed between the species of host and parasite and indicated the biologic maladjustment of the parasite to the host

PEARL ZEEK

THE PASSAGE OF LIVING BACTERIA THROUGH THE INTESTINAL WALL LLOYD  
ARNOLD, *Am J Hyg* 8 604, 1928

The bacterial flora of the small intestine can be altered by diet and also by climatic changes. Disturbances in the heat regulatory mechanism of the animal cause a qualitative and quantitative difference in the flora of the upper half of the small intestine. These changes are intimately associated with an inhibition of the normal bactericidal power of the small intestine. This allows the cecal flora to ascend into the upper part of the alimentary tract, and interferes with the destruction of ingested bacteria.

Sudden alkalinization of the upper part of the small intestine, in the presence of certain kinds of protein material or bile, allows viable bacteria to pass through the wall of the intestinal tract and appear for a short period of time in the thoracic duct. It is thought that these changes are brought about by alterations in the equilibrium of the autonomic nervous system.

PEARL ZEEK

A CRITIQUE ON ARTIFICIAL PNEUMOTHORAX IN PULMONARY TUBERCULOSIS  
HENRY SEWALL, *Am Rev Tuberc* 18 117, 1928

The observations set forth appear to offer solid ground for deductions as to the course of events within the thorax after complete artificial collapse of the extensively diseased left lung. While the pendular motions of the whole mediastinum and the arclike deviations of the flexible and free portions of the mediastinal pleurae have the same cause and are quantitatively similar when unmodified by adhesions, these motions are largely dissociated at a later stage of the clinical history. Comparatively early in the treatment with pneumothorax there was wide pendular swinging of the whole mediastinum. Later in the course of treatment, both movements become progressively restricted, the pendular movement to a greater degree. Moreover, the tendency to complete elimination of the pneumothorax cavity is shown by the increasing mean inclination of the mediastinum towards that side. The obliteration of this cavity must depend primarily on reexpansion of the collapsed lung, in default of which there is approximation and increased inclination of the ribs and ascent of the diaphragm on the affected side, added to which and probably most important of all, is deviation of the plane of the mediastinum, which the stiffening and adhesions make progressively more difficult. Keeping pace with this displacement is compensatory hypertrophy of the contralateral lung.

An interesting outcome of these experimental observations was the demonstration that approximately isolated costal breathing had a marked influence on the pendular swing of the mediastinum as a whole, while pure diaphragmatic breathing had comparatively little effect. The reverse was true in the case of bulging of the flexible mediastinal pleurae, dependent on the relaxation or tautness, respectively, of the membranes with the ascent and descent of the diaphragm. With the lapse of time and progressive diminution of the pneumothorax cavity, the pendular motions of the mediastinum became relatively more restricted than the vertical motions of the lung which are activated by the diaphragm.

H J CORPER

FACTORS IN THE PATHOGENESIS OF TUBERCULOSIS ALLEN K. KRAUSE, *Am Rev Tuberc* 18 208, 1928

In following the many varied threads of this complicated and tangled skein that leads to the pathogenesis of tuberculosis, one should ever keep in mind that between the time the offending bacilli are received and that of pathogenesis, the natural history of tuberculous infection rarely discloses the disease as pursuing an uninterrupted course. Even infected infants who fall ill (and only the lesser

THE PLASMA IN SEVERE DIABETIC ACIDOSIS A F HARTMANN and D C DARROW, J Clin Investigation 6 257, 1928

The composition of the blood plasma was studied in six cases of severe diabetic acidosis and also during the period of recovery. It was shown that marked concentration of the plasma occurred with but slight diminution of total base. The decrease of bicarbonate and chloride was relatively greater than the increase of ketone acid and protein. Treatment with water and insulin, with or without carbohydrate, restored the bicarbonate and  $p_H$  relatively slowly at first, and the addition of salt solution aided but little in bicarbonate recovery. The combination of sodium bicarbonate with water, insulin, carbohydrate and sodium chloride provided a rapid and complete relief from acidosis.

H R FISHBACK

THE  $p_H$  OF THE URINE UNDER VITAL CONDITIONS A BECK and H J LAUBER, Klin Wchnschr 7 2241, 1928

$p_H$  determinations of the urine with indicators is often without regard for the carbon dioxide tension. A shift in the  $p_H$  to a more alkaline (or less acid) reaction occurs promptly when carbon dioxide escapes, greater with alkaline urines than acid. Temperature variations also influence markedly the carbon dioxide tension and consequently the  $p_H$ .

EDWIN F HIRSCH

### Microbiology and Parasitology

CYTOLYSIS IN THE CEREBROSPINAL FLUID IN ACUTE POLIOMYELITIS G LYON, Am J Dis Child 36 40, 1928

Cytolysis has been observed in the early pleocytoses of acute poliomyelitis, which is more active toward the multilobed elements than toward the mononuclear elements.

Proof is given of the advisability of making cell counts of the spinal fluid immediately after lumbar puncture in all cases in which there may be a possibility of poliomyelitis.

A pleocytosis consisting of 50 per cent or more of multilobed cells, occurring in a clear fluid, is suggestive of acute poliomyelitic infection. When in the course of from twenty-four to thirty-six hours, the lumbar puncture is repeated and there is a fall in the total cell count with a shifting of the differential count to a mononucleosis of 90 per cent or more, one may be certain that the condition is one of poliomyelitic infection. This cellular response is pathognomonic, as it has not been observed in the spinal fluid in other conditions.

AUTHOR'S SUMMARY

INFECTION OF THE CONJUNCTIVA AND CORNEA OF GUINEA-PIGS FOLLOWING THE APPLICATION OF VIRULENT DIPHTHERIA BACILLI MARGARET BEATTIE, Am J Hyg 8 502, 1928

The application of diphtheria bacilli to the previously irritated eyes of guinea-pigs for the purpose of detecting the immunity of animals immunized against diphtheria is not reliable, since 50 per cent of normal animals tested were not infected.

PEARL ZECK

INFECTION WITH STRONGYLOIDES STERCORALIS J H SANDGROUND, Am J Hyg 8 507 1928

Dogs and cats of all ages were successfully infected with *Strongyloides stercoralis* secured from a human patient. The animals showed certain decided differences in susceptibility to the disease and to its duration. The infections disappeared spontaneously and were followed by the acquired immunity which, in dogs, lasted for more than six months. The development of immunity was thought to be



intimately associated with the relationship that existed between the species of host and parasite and indicated the biologic maladjustment of the parasite to the host

PEARL ZEEK

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H J CORPER

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In following the many varied threads of this complicated and tangled skein that leads to the pathogenesis of tuberculosis, one should ever keep in mind that between the time the offending bacilli are received and that of pathogenesis, the natural history of tuberculous infection rarely discloses the disease as pursuing an uninterrupted course. Even infected infants who fall ill (and only the lesser

number do) will be found to go weeks and months with an inactive infection before a breakdown, the child months and years, and the adults years and decades. If there were no other guiding facts this circumstance alone should show that, in the majority of cases, neither native character of tissue nor kind of dosage of bacillus is decisive in establishing the pathogenesis of tuberculosis, contributory though each may be to the result. The net result of this inquiry is to suggest that from the first meeting of virulent germ and susceptible host in most cases there results a tissue graft which, if placed in the tissues of the animal man who was living a normal existence, would, because of a prompt acquisition of allergy and immunity, go the way of limited development and at last obsolescence. But civilized man has drifted far from the life of man the animal, and in the journey has been and is subjecting his ingrafted tubercle to varied forces that promote its growth and spread. Back of every awakening of tubercle, back of every nurturing of its evolution, is an experience or succession of experiences that have promoted its continued existence of progression. Common observation teaches us that such an experience, regarded physiologically, is characteristically of a stressful nature. Whatever may be stressful is to be viewed in its relations to the individual. The ultimate solution of the problem of pathogenesis of tuberculosis in human beings must be sought where the sick human being is—in the clinic—and the answer obtained from the story of the human being himself. So far, his imperfect accents all speak one way, to the effect that it is what he has done and what has happened to him since infection that have been most momentous. Environment or individual experience has swung toward or away from pathogenesis the balance formed by the initial meeting of germ and host, and soon affected by allergy and immunity.

H J CORPER

A STUDY OF TUBERCULOUS LESIONS IN THE LUNG OF A NEGRO CHILD NINE WEEKS OLD WILLIAM SNOW MILLER, *Am Rev Tuberc* 18 373, 1928

The lung on which this study was made was that of a negro girl, aged 9 weeks, who had been ill for six weeks. Careful reconstructions were made. The article has profuse illustration, including stereoscopic pictures. With the exception of one small area of tuberculous bronchopneumonia, miliary tubercles formed the only lesions in the region studied. The infection was conveyed from some source, as yet undetermined, through the arterial blood stream. The tubercles had developed in the capillary bed between the pulmonary artery and the pulmonary vein. The primary infection seemed to be in the lymphoid tissue associated with the pulmonary vein, this receives its blood supply from the pulmonary artery. The lymphatics were not involved in the tuberculous lesion. All the valves found in the lymphatics were situated less than 2 mm below the surface of the pleura and opened towards the pleura. This means that from a narrow peripheral zone of the lung, the lymph must drain toward the pleura, but leaves unsettled the direction of flow from deeper portions, although it must be assumed that from the central portion the flow is toward the hilum.

H J CORPER

THE DURATION OF LIFE IN PULMONARY TUBERCULOSIS WITH CAVITY HARRY L BARNES and LENA R P BARNES, *Am Rev Tuberc* 18 412, 1928

Of 1,454 patients with cavity which were reviewed, 80 per cent died within one year, 82 per cent within two years, 85 per cent within three years, 90 per cent within five years and 95 per cent within fifteen years. The average duration of life of 270 patients with cavities, from the appearance of the signs of cavities until death, was 15.8 months. Had the remaining survivors died on the day the statistics were compiled, it would have raised the average duration to twenty-four months. In 99 per cent of 616 cases of cavity diagnosed by roentgenogram, tubercle bacilli were found in the sputum. A family history of tuberculosis, a history of hemoptysis, or the age of the patient did not materially affect the prognosis. Only one of fifty-seven colored patients survived for three years. The average duration of life was sixteen months in males and fourteen months in females. The percentage of survivors after periods of three and five years, among patients with a pulse

rate of less than 90 was five times as great as among patients with a pulse rate of more than 100. The percentage of patients who survived for one year was more than three times as great, and of those who survived for five years was eight times as great, among patients with temperature of less than 99 F as among patients with temperatures of more than 100 F. The survivors among patients with cavity of the right lung were slightly more numerous and lived slightly longer than those among patients with cavity of the left lung. The percentage of survivors for one and three years, respectively, was in direct relation to the amount of pulmonary disease. The duration of life bore a direct relation to the number of cavities. Of 17 patients with more than three cavities, none survived a year. Eighty-eight per cent of patients with cavities larger than 7 cm died within a year. Among cases of small cavities (from 1 to 2 cm) there were about 50 per cent more survivors at the end of the first year than there were in cases of large cavities (2 to 15 cm), but 82 per cent of the patients with small cavities died within three years. Cases of honeycombed cavity were about as serious in outlook as cases of cavities of average size. Patients with well formed cavity walls had a slightly longer duration of life. Patients with well marked roentgen evidence of calcification had a greater percentage of survivors. Among patients with roentgen evidence of pleural thickening over the greater part of one lung there was a higher percentage of survivors. Of the 1,454 cases with cavities reviewed, the patients in 1,244, or 85 per cent, are dead, the average duration of life was more than twelve months.

H J CORPER

TUBERCULOUS GRANULOMA OF A BRONCHUS PHILIPP SCHONWALD, *Am Rev Tuberc* **18** 425, 1928

A case of tuberculosis is presented, in which a tuberculous laryngitis and a granuloma in the mucosa of the right bronchus, at the bifurcation, developed after a spontaneous cure of tuberculous peritonitis. The laryngitis improved greatly, but the narrowing of the right bronchus caused stagnation of purulent material in the right lung, followed by atelectasis of the right lower lobe, the spread of the infection throughout the entire right lung and, finally, spontaneous pneumothorax of the right upper lobe. The mucus, presenting almost a pure culture of tubercle bacilli, was of extreme viscosity. Its stagnation, after the pneumothorax had prevented cough, brought about asphyxiation.

H J CORPER

THE REACTIONS OF THE WHITE BLOOD CELLS OF THE GUINEA-PIG FOLLOWING INOCULATION WITH HUMAN TUBERCLE BACILLI WILL CAMP, F H LUTON, EDNA H TOMPKINS and R S CUNNINGHAM, *Am Rev Tuberc* **18** 462, 1928

Intraperitoneal inoculations of the guinea-pig with tubercle bacilli from human beings invariably resulted in fatal infection. After inoculations of 50,000,000 or more bacilli, the tenure of life averaged three weeks, after inoculations of smaller numbers, life was irregularly prolonged. The pathologic changes in all the animals were characteristic of a generalized tuberculosis and showed three outstanding features. 1 The tissues in the early infections showed the characteristic picture of tubercle, that is, collections of monocytes and epithelioid cells which contained bacilli and were more or less intermingled with lymphocytes. 2 The tissues in the older infections presented much fibrosis, and often necrosis superimposed on the earlier single tubercles. 3 The liver invariably presented massive infection. It was consistently far more involved than is usual in tuberculous infection of the human being or the rabbit. In the older infections, the parenchymatous cells were tremendously vacuolated and filled with droplets of fat.

The blood showed definite changes following inoculation. 1 The lymphocytes decreased in number. The diminution was most marked toward exitus. 2 The monocytes increased in number and developed many of the characteristics of epithelioid cells. The increase was most marked toward exitus. 3 The magnitude of these reactions was independent of the number of bacilli with which the animals

were inoculated 4 These reactions began earlier after inoculation when large numbers of bacilli were inoculated than when smaller numbers were inoculated 5 These reactions were found to be an index of infection and to parallel the progress of the disease 6 The changes in the total white cell counts and in the polymorphonuclear neutrophils bore no constant relationship to the date of inoculation, or to the reactions in the monocytes and lymphocytes

H J CORPLER

THE SIGNIFICANCE OF POSITIVE AND NEGATIVE SPUTUM FINDINGS IN PULMONARY TUBERCULOSIS MAX PINNER and WAITER I WELNER, *Am Rev Tuberc* **18** 490, 1928

In a study of more than 500 adult patients with active pulmonary tuberculosis tubercle bacilli were found in the sputum in over 99 per cent The absence of tubercle bacilli in the sputum of patients with pulmonary tuberculosis almost always indicates healing Sputum free from tubercle bacilli has a much greater diagnostic and prognostic significance than is represented in the usual textbook Every sanatorium could well invest in facilities for the complete examination of sputums from all patients

H J CORPLER

CARBOHYDRATE CONTENT OF THE ALCOHOL-SOLUBLE ANTIGEN OF TUBERCLE BACILLI KATHRYN KNOWITON and MAX PINNER, *Am Rev Tuberc* **18** 502, 1928

The antigenic strength of the alcohol-soluble antigen of tubercle bacilli is apparently independent of both proteins and the specific carbohydrate This fact leaves but little doubt that the antigen is of lipid nature

H J CORPLER

WATER-SOLUBLE PROTEIN AND CARBOHYDRATE IN TUBERCLE BACILLI FROM VARIOUS SOURCES TRIAT B JOHNSON and ALICE G RENZI, *Am Rev Tuberc* **18** 505, 1928

Four specimens of tubercle bacilli from different sources have been examined for their content of active protein no 304 and carbohydrate While the yield of the protein is very low when autoclaved cells are used, the carbohydrate is still obtainable, but in reduced amounts Both combinations apparently undergo change when the cells are heated at 100 C or more A technique is described for separating both fractions from a single unit of cells, and a modified technique is given for extracting the sugar fraction alone

H J CORPLER

A DEATH IN CHICAGO IN SEPTEMBER, 1928, FROM INFLUENZA EDWIN F HIRSCH and E R LE COUNTE, *J A M A* **91** 1186 (Oct 20) 1928

A case is described in which the changes in the lungs appeared to be characteristic of those observed in epidemic influenza "The distribution of the disseminated pneumonia, the great increase in the weight of the lungs, the characteristic purple, sharply limited 'buttons' of subpleural hemorrhage, the even, thin deposit of hyaline on the lining of the smaller air passages and death on the second day all conform to the characteristic manifestations of the disease with which we became so familiar in 1918"

THE RELATION OF VIRULENCE IN PNEUMOCOCCI TO DISSEMINATION, WITH A COMPARISON OF VIRULENCE OF THE DIFFERENT TYPES OF PNEUMOCOCCI IN VARIOUS PATHOLOGICAL CONDITIONS C H WHITTIE, *J Hyg* **27** 412 1928

Lobar pneumonia, bronchopneumonia and empyema arising in previously healthy subjects are caused by strains of high virulence Lobar pneumonia is caused by strains of the highest virulence, bronchopneumonia by strains of a rather low

virulence Empyema is caused by strains the virulence of which is characteristic of either lobar pneumonia or bronchopneumonia The virulence requisite for the development of lobar pneumonia in man is the same as for the development of lobar pneumonia in rabbits

IRVING H SCHROTH

PROTEUS AMMONIAL THOMAS B MAGATH, J Infect Dis **43** 181, 1928

Detailed description is given of eighteen cultures of *Proteus ammoniac* from urine Since the organism does not ferment dextrose, it is proposed to modify the generic characterization of the genus *Proteus*

AUTHOR'S SUMMARY

THE TREATMENT OF TYPHOID FEVER WITH DETOXICATED VACCINE W B WHERRY, T J LE BLANC, L FOSHAY and R THOMAS, J Infect Dis **43** 189, 1928

*Bacillus typhosus* antigen can be detoxicated to a considerable degree by treating it with formaldehyde, according to Ramon's method From about 82 to 164 millions of treated bacilli may be injected subcutaneously and daily into a patient with typhoid fever, irrespective of the apparent severity of the disease without any harm Twenty-eight patients with typhoid fever (bacteriologic diagnosis) were treated in this manner in Cincinnati and in Mexico City by daily subcutaneous inoculations with from 82 to 164 millions of bacilli treated with formaldehyde The results of this treatment, along with data collected from 68 control cases, seem to show that the course of the disease is shortened, the temperature uniformly showing a tendency to drop to normal after the seventh or eighth dose and then coming to normal by irregular lysis The average duration of the fever in the treated patients was 27.5 days, while that in the controls was 39 days The incidence of complications seems decreased 7 per cent in the treated, and 36 per cent in the untreated patients Convalescence is shortened for those patients treated early in the course of the disease The death rate is decreased from 10 per cent for the untreated to zero for the treated patients It is to be hoped that others will help to collect enough data to make a rigid statistical analysis possible

AUTHORS' SUMMARY

REPLACEMENT OF POTASSIUM BY OTHER ELEMENTS IN CULTURE MEDIUMS C H BOISSEVAIN, J Infect Dis **43** 194, 1928

The acidfast bacteria that were tested grew well on a simple synthetic medium All needed potassium or rubidium for their growth, the minimum concentrations were 0.001 per cent potassium chloride and 0.002 per cent rubidium chloride

Cesium, sodium, lithium or the radioactive elements or combinations of the two cannot replace potassium in synthetic culture mediums

Continuous exposure to the roentgen rays for 168 hours does not kill smegma bacilli and does not favor their growth

Among the gram-positive organisms, only a soil bacillus not previously described grew freely on the synthetic medium, it needed the same amount of potassium as the acidfast bacteria

Among the gram-negative organisms examined, *Bacterium coli* and *Bacterium paratyphosus* B grew freely on the synthetic medium, they did not need potassium

AUTHOR'S SUMMARY

FILTRABLE FORMS OF THE TUBERCLE BACILLUS FRANK B COOPER and S A PETROFF, J Infect Dis **43** 200, 1928

We have failed to obtain growth from Berkefeld filtrates prepared from pure cultures of tubercle bacilli or from sputums which contain large numbers of this organism, and we have failed to observe any demonstrable tuberculosis leading to a progressive disease, either in the mothers inoculated with such filtrates or

in the offspring. We have been able, however, to demonstrate acidfast granules in such offspring, and typical acidfast organisms were found in about 36 per cent of the full grown guinea-pigs which had received filtrates. However, we have also found these acidfast organisms in the lymph nodes of 33 per cent of apparently normal animals which have never been inoculated with this material. The positive results reported by others in all probability may be due to organisms which occasionally can pass through the Berkefeld filter. Several factors may play a part in such passage, as follows: imperfect filters, the pressure used for such filtration, the medium employed, and the electro-charge of the candle.

## AUTHORS' SUMMARY

CHRONIC LOCALIZED STREPTOCOCCUS INFECTIONS IN DOGS. G. BLRNICE RHODES and CARL W. APFILLBACH, J. Infect. Dis. **43** 215, 1928.

Chronic abscesses were produced in the spleen and the sacrospinalis muscles of dogs by imbedding pieces of dead bone infected with *Streptococcus scarlatinae*, and in one instance with *Staphylococcus aureus*.

These focal infections resemble those occurring in human beings so far as chronicity and alternating active and quiescent periods of infection are concerned. Few complications like those occurring in human beings have so far been observed, although one dog had acute interstitial nephritis and two had iridocyclitis. We believe that this method is adaptable in many instances in which attempts are made to reproduce infectious diseases experimentally in animals.

## AUTHORS' SUMMARY

DODERLEIN'S BACILLUS. *LACTOBACILLUS ACIDOPHILUS*. STANLEY THOMAS, J. Infect. Dis. **43** 218, 1928.

Doderlein's vaginal bacillus is *Lactobacillus acidophilus*. This organism is present in less than 10 per cent of the normal vaginas of children. It gets into the vagina by exterior passage from the intestinal tract, and can be introduced into the vagina by feeding a culture by mouth. It lives and develops acid either from a secretion of the vagina, from conveyed fermentable intestinal material or from both. The organism is not present in the vagina in cases of gonococcal vaginitis. The organism has an inhibiting effect on the growth of the gonococcus in vitro, vaginal implantation of *Lactobacillus acidophilus* may present a rational cure for gonococcal vulvovaginitis and other gonococcal infections.

## AUTHOR'S SUMMARY

STUDIES ON THE METABOLISM OF THE ABORTUM-MELITENSIS GROUP. JAMES G. McALPINE and CHARLES A. SLANETZ, J. Infect. Dis. **43** 232, 1928.

By the addition of from 5 to 10 per cent of carbon dioxide to bell jars containing inoculated plates, the growth of the bovine strains of *Bacterium abortum* which had been acclimated to aerobic conditions was markedly accelerated. On the other hand, this amount of the gas had a more or less inhibitory action on *B. abortum* strains of porcine and human origin, and on *Bacterium melitensis*. This acceleration of growth for the bovine strains and inhibition for the porcine and human strains of *B. abortum* and of *B. melitensis* was apparently not due to change in the hydrogen ion concentration of the mediums. Total exclusion of carbon dioxide rendered the members of the abortum-melitensis group inert and unable to proliferate.

## AUTHORS' SUMMARY

EXPERIMENTS RELATING TO THE PATHOLOGY AND ETIOLOGY OF MEXICAN TYPHUS (TABARDILLO). H. MOOSER, J. Infect. Dis. **43** 241 and 261, 1928.

Over 90 per cent of the male guinea-pigs inoculated with the virus of Mexican typhus (tabardillo) presented more or less pronounced swelling and reddening of the scrotum, which was due to extensive specific lesions in the tunica cremasterica,

tunica vaginalis and testicles The endothelial lining of the tunica vaginalis reacts exactly in the same manner to the presence of the virus of typhus as does the vascular endothelium There was evidence that a considerable amount of virus was present in the swollen tunica and that it had accumulated there within the endothelial cells during the period of incubation

A minute intracellular diplobacillus has been demonstrated in sections and smears of the proliferated tunica vaginalis of guinea-pigs reacting to the virus of Mexican typhus (tabardillo) Considerable evidence is given that this diplobacillus is the causative agent of typhus

AUTHOR'S SUMMARY

RECENT CASES OF UNDULANT FEVER IN NEW YORK STATE RUTH GIBBLRT  
and MARION B COLFMAN, J Infect Dis **43** 273, 1928

This investigation demonstrates that cases of undulant fever are not uncommon and that they are distributed rather generally throughout New York State In none of the cases studied was there a history of contact of patient with goats or hogs, but 14 patients were known to have used raw cow's milk In nine instances abortions were found to have occurred in the herds from which the milk was obtained A consideration of the data available indicates three possible reasons why cases of undulant fever are not reported more frequently in districts where unpasteurized milk is obtained from herds in which contagious abortion is prevalent Many of the severe infections have probably been diagnosed as atypical cases of typhoid fever, influenza, or even as tuberculosis or malaria, mild forms may have presented so few symptoms that physicians have not been consulted, and the blood from some cases of undulant fever may not have agglutinated cultures of *Bacterium melitensis* or *Bacterium abortum*

AUTHORS' SUMMARY

DETOXIFYING, DIFFUSING, GERMICIDAL, AND SURFACE TENSION DEPRESSING  
PROPERTIES OF SOAPS FORREST R DAVISON, J Infect Dis **43** 292, 1928

Twelve common soaps were prepared and their detoxifying, diffusing, germicidal and surface tension depressing properties were studied Soaps possessing high detoxifying ability diffuse readily, are highly germicidal, but are correspondingly low depressants of surface tension

AUTHOR'S SUMMARY

OBSERVATIONS ON THE MORPHOLOGY AND MOTILITY OF FUSIFORM BACILLI  
C C KAST, J Lab & Clin Med **13** 112, 1928

No evidence of spirochetal forms was seen by Kast in a pure culture of fusiform bacilli grown anaerobically in medium of varying hydrogen ion concentration containing fresh tissue The formation of colonies and the division of fusiform bacilli were observed in a micro slide preparation Motile fusiform bacilli, together with nonmotile forms were found in material taken directly from pathologic conditions and in mixed cultures in Schereschewsky's coagulated horse serum medium

S A LEVINSON

THE ACTION OF VIBRION SEPTIQUE AND B WELCHII TOXIN ON ISOLATED  
ORGANS G A H BUTTLE and J W TREVAN, Brit J Exper Path **9** 182,  
1928

Experiments dealing with the actions of *Vibrio septique* and *Bacillus welchii* toxins on involuntary muscle in vitro reveal the following facts 1 The toxin of *V. septique* is destroyed by bubbling air, oxygen or hydrogen through its solution and its action is reversible by washing with Ringer's solution and adding a large amount of serum 2 The concentration of toxin producing effects on smooth muscle in aerated Ringer's solution is shown to be of the same order as that in the blood of a rabbit receiving an average lethal dose 3 A small dose of *V. septique* toxin added to a bath of oxygenated Ringer's solution containing a piece of uterus renders the tissue insensitive to the action of larger doses of either

## ARCHIVES OF PATHOLOGY

*V. septique* or *B. welchii* toxin 4 The important part of the action of the two toxins is specific in that they are neutralized only by the appropriate antiserums. Titrations of the antitoxin potency of serums are described

PEARL ZEEK  
J C G

THE PROPAGATION OF VACCINE VIRUS IN THE RABBIT DERMIS  
LEDINGHAM and D McLEAN, Brit J Exper Path 9 216, 1928

A technic is described by which the vaccine virus is adapted to growth in the dermis of the rabbit and subsequently is passed successively from dermis to dermis. The growth has been measured quantitatively by titration of successive dilutions of pulp prepared from excised dermal lesions and it is shown that an inoculum by proliferation in the dermis may develop at least 100,000 times its original content of minimal infecting doses. Dermal virus, by virtue of its intrinsic freedom from bacteria, is eminently suitable for use in many spheres of the study of virus

PEARL ZEEK  
Ann

IS *TREPONEMA PALLIDUM* A STAGE IN THE LIFE CYCLE OF THE VIRUS OF SYPHILIS?  
C LEVADITI, R SCOEHN and M V SANCHIS-BAYARRI, Ann de l'Inst Pasteur 42 475, 1928

Histologic studies with rabbit syphilis indicate the presence of cellular inclusions with affinity for silver stain and without any morphologic resemblance to the *Treponema pallidum* during latent stages when lymphatic ganglions are demonstrably ineffective. The existence of a resistant and inapparent stage in a postulated life cycle of the *Treponema* seems to the authors highly probable

M S MARSHALL

THE BACTERIAL FLORA OF THE SPUTUM IN ASPIRATION PNEUMONIA FOLLOWING HEMOPTYSIS  
A FINKLI-KARPOVSKY, Beitr z klin d Tuberk 69 594, 1928

Hemoptysic aspiration pneumonia usually shows large numbers of gram-positive and encapsulated diplococci in the sputum. They are most numerous at the end of the first week and usually disappear in the fifth or sixth week. While the diplococci are present, tubercle bacilli usually disappear. The reappearance of tubercle bacilli in the sputum, while the clinical signs of pneumonia still persist, indicates the tuberculous character of the pneumonia

MAX PINNER

THE INFLUENCE OF RAREFIED AIR ON THE DEVELOPMENT OF EXPERIMENTAL TUBERCULOSIS IN GUINEA-PIGS  
S DEL RIO, Beitr z klin d Tuberk 69 636, 1928

Ten guinea-pigs were infected subcutaneously with tubercle bacilli and five of them were kept at a barometric pressure of 200 mm below the normal; the other five were kept at normal barometric pressure. The animals which lived under normal pressure gained in weight, and showed a more extensive tuberculosis of the spleen. Otherwise there was no noticeable difference between the two groups of animals

MAX PINNER

MIXED INFECTION IN PULMONARY TUBERCULOSIS  
MOROSOWA, Beitr z klin d Tuberk 69 656, 1928

Secondary infection in pulmonary tuberculosis is rare and diagnosis should be made by blood culture. Even in the preagonal phase, mixed infections do not occur frequently. The temperature does not permit one to make a diagnosis of mixed infection. In order to obtain a culture of a secondary organism, the sputum must be thoroughly washed

MAX PINNER



TUBERCULOSIS OF THE SPLEEN AND POLYCYTHAEMIA VERA E SACHS, Beitr  
z klin d Tuberk **69** 699, 1928

The clinical history and necropsy observations on a patient, aged 58, are reported. The clinical diagnosis was polycythemia vera with a blood count as high as 11,000,000. The necropsy revealed a rather recent hematogenous tuberculosis of the spleen and the liver. This case leaves no doubt that the tuberculosis developed years after the polycythemia and that it did not play any causative role in the development of the former.

MAX PINNER

RATIN INFECTION IN MICE AND TREATMENT WITH MLTALS J CRSKOV and  
ADAM SCHMIDT, Ztschr Immunitätsforsch u exper Therap **55** 69, 1928

The injection of salts of cesium and manganese into mice infected with ratin did not prevent the development of bacteremia. In the animals so treated improvement set in about the third day while in the untreated control animals death occurred after four or five days. The results appear to indicate a curative action by the salts.

JOHN HAYS BAILEY

THE INFLUENCE OF THE RETICULO-ENDOTHELIAL SYSTEM ON THE PROPHYLACTIC EFFECT OF ACETARSONE (STOVARSON) AGAINST SPIROCHETES P L RUBENSTEIN, Ztschr f Immunitätsforsch u exper Therap **55** 107, 1928

In normal mice infected with *Spirillum obermeieri* 92 per cent were sterilized by acetarsone after blocking of the reticulo-endothelial system with ferric saccharate, 57.5 per cent of the mice were apparently sterilized by acetarsone stovarsol but 12.7 per cent died later from relapsing fever. After splenectomy, with or without blockage of the reticulo-endothelial system, acetarsone had no therapeutic action.

JOHN HAYS BAILEY

THE ACTION OF FILTRATES OF STREPTOCOCCI ON THE CORNEA OF THE RABBIT O KIRCHMER, Ztschr f Immunitätsforsch u exper Therap **55** 157, 1928

On injecting small doses of filtrates of cultures of various strains of streptococci into the cornea of rabbits, a reaction developed in the majority of instances, this consisted of clouding of the cornea, conjunctivitis and the formation of pannus. This reaction, which followed multiple injections of from 0.1 to 0.2 cc of filtrate, diluted 1:20 (about fifty skin test doses), spaced from six to seven days apart, did not appear until after the second or third injection had been given. The conjunctivitis was usually marked, reaching its height in from two to three days. The pannus reached a climax after four or five days and slowly receded until after two to three weeks only a slight turbidity and some pannus was present.

The reaction was obtained with a commercial scarlet fever toxin, and filtrates of broth cultures of the Dochez and Riess strains of hemolytic streptococci, but not with filtrates of a broth culture of a nonhemolytic streptococcus isolated from mastitis. As control tests, the same amount of filtrate, heated at 100 C for one hour, was injected into the cornea of the other eye. No reaction except a transient conjunctivitis resulted from these injections. The author believes that the reaction obtained was an anaphylactic response and not due to a particular substance primarily toxic for the cornea of rabbits.

JOHN HAYS BAILEY

## Immunology

IMMUNOLOGIC STUDIES ON VARIOUS FRACTIONS OF TUBERCLE BACILLI MAX PINNER, Am Rev Tuberc **18** 497, 1928

Various protein, phosphatid and fat fractions have been investigated as to their immunologic behavior. The results with these chemically well defined fractions confirm essentially previous similar work done with less pure materials. Probably the most important result is the fact that a phosphatid fraction was found to be a true antigen.

H I CORPER

THE VERNES FLOCCULATION TEST FOR TUBERCULOSIS RESULTS OF 250 CASES  
ADELAIDE B BAYTIS, *Am Rev Tuberc* **18** 513, 1928

The Vernes flocculation test is of value in the detection of active tuberculosis. The test is of even greater value as a guide in treatment, especially in regulating the mode of life in relatively quiescent cases. When high readings are obtained in patients with doubtful diagnosis, a thorough reexamination of all the evidence is demanded. In patients who present evidence of other disease and in whom tuberculosis has not been suspected, a high reading will direct attention to the possibility of this disease, and a low reading would tend to eliminate tuberculosis from consideration. The observations on asthmatic patients under tuberculin treatment suggest a behavior which parallels that of a tuberculous patient to some extent. The Vernes flocculation test is not specific for tuberculosis in a bacteriologic sense, but it is an extremely precise and delicate test, superior to other serologic tests which have been employed in tuberculosis. It is a valuable aid in diagnosis and as a guide in the treatment of the tuberculous patient.

H J CORPER

SURFACE TENSION OF SERUM AS AFFECTED BY THE PRECIPITIN REACTION  
SUSAN GRIFFITH RAMSDELL, *J Exper Med* **48** 615, 1928

An attempt to find evidence of a denaturing effect of the precipitin reaction on either the antigen or the immune serum, through the study of surface tension by use of the du Nouy tensiometer, yielded entirely negative results.

AUTHOR'S SUMMARY

BACTERIOPHAGE STUDIES RALPH S MUCKENFUSS, *J Exper Med* **48** 709 and 723, 1928

*Mode of Action of Antibacteriophage Serum*—Each bacteriophage is a specific antigen. The antibodies against the bacteriophage are independent of those against the bacterial substrate used in preparing the phage. The reaction of neutralization is closely analogous to that of the neutralization of toxin by antitoxin. The serum of mice experimentally infected with mouse typhoid (MT<sup>2</sup>) did not become capable of neutralizing phages acting on the infecting organism. The use of the reaction of neutralization of bacteriophage in the diagnosis of disease as proposed by Sonnenschein seems impractical.

*The Production of Phage from Bacterial Cultures*—The phenomenon of phage production by one bacterial culture for another of different sort has been reproduced experimentally. This phenomenon results from phage carried with the culture, and not from the spontaneous appearance of phage in a culture previously free from it. Animals immunized against the lysogenic bacteria may develop antibodies that neutralize the phage carried. The development of neutralizing antibodies on immunization with a bacterial culture is evidence of the presence of bacteriophage in the culture. The failure of such antibodies to appear on immunization with bacteria does not necessarily indicate that bacteriophage is not present.

AUTHOR'S SUMMARIES

ON THE INHERITANCE OF AGGLUTINOGENS OF HUMAN BLOOD DEMONSTRABLE BY IMMUNE AGGLUTININS K LANDSTEINER and PHILIP LEVINE, *J Exper Med* **48** 731, 1928

The heredity of two agglutinable structures demonstrable by immune agglutinins was studied in 166 families. From the data collected it is evident that one deals with a case of mendelian inheritance. The main result of the studies is the demonstration that it is feasible to investigate the heredity of serologic structures of human blood other than the group agglutinogens. Irrespective of the ultimate theory it seems probable that the properties M and N do not appear in the offspring when they are absent in both parents—a conclusion substantiated by the examina-

tion of ten families with forty-six children. These observations offer the prospect of forensic application to cases of disputed paternity and, in our opinion, a correct decision could already be given, at least with great probability, provided the reagents are available and the method properly applied. Of course, further work is needed before the test can be adopted as a routine procedure.

## AUTHORS' SUMMARY

A PRECIPITIN TEST IN INTESTINAL SCHISTOSOMIASIS W. H. TALIAFERRO, W. A. HOFFMAN and D. H. COOK, *J. Prev. Med.* **2** 395, 1928

A specific antigen was prepared by aqueous extraction of the dried livers of snails (*Planorbis guadeloupensis*) containing larval stages of *Schistosoma mansoni*. Precipitin tests of the serum of patients infected with *S. mansoni* or syphilis gave a larger percentage of positive reactions in the former. The active principle of the aqueous extract is precipitated with the albumin fraction by complete saturation with ammonium sulphate. Control antigens from the uninfected livers of snails gave negative reactions with serum from patients infected with *S. mansoni*.

AN INTRADERMAL REACTION IN EXPERIMENTAL TRICHINIASIS GEORGE W. BACHMAN, *J. Prev. Med.* **2** 513, 1928

Thirty-three rabbits and twelve guinea-pigs infected with *Trichinella* showed a local skin reaction, specific in character, following the intracutaneous injection of *Trichinella* protein. The control tests with the diluent alone were negative with eight exceptions (eight tests on four rabbits). Twenty-five of the rabbits and all of the guinea-pigs, when tested before infection, gave uniformly negative skin reactions. Five normal rabbits and three normal guinea-pigs, after multiple skin tests, showed positive skin tests toward the end of the testing. These were generally rather weak, but in one guinea-pig a +++ reaction was obtained. As is evident from the tables, typical skin reactions appeared as early as the second day after infection, but in view of the fact that the preliminary skin test may have caused a local hypersensitivity, it is probably safer to conclude that typical skin reactions appear within the first week after infection. The reaction seems specific to *Trichinella* proteins since fairly negative results were obtained with *Ascaris* protein. Precipitin tests on twenty-two rabbits confirm a previous conclusion that specific precipitins are not demonstrable until from twenty to thirty days after infection. As a method of diagnosis, the skin reaction is easy and much more practical than the precipitin test since typical skin reactions appear from twenty to thirty days before the precipitins are demonstrable in the blood stream.

## AUTHOR'S SUMMARY

EXPERIMENTAL SENSITIZATION PER VAGINAM WITH PROTEINS FROM MALE GONADS DAVID I. MACHT, *J. Urol.* **20** 733, 1928

After a successful series of experiments on sensitization of guinea-pigs by instillation of blood serum into the vagina were performed, a series of experiments were made with instillations of fresh prostatic and testicular emulsions and positive evidence of sensitization produced in guinea-pigs in this way has been obtained.

## AUTHOR'S SUMMARY

THE TREATMENT OF PULMONARY TUBERCULOSIS WITH A RESIDUAL ANTIGEN C. E. JENKINS, *Brit. J. Tuberc.* **22** 126, 1928

The author prepares a residual antigen from cultures of human and bovine strains of tubercle bacilli by a rather elaborate method of ether extraction, sodium hydroxide digestion and treatment with pepsin and hydrogen peroxide. The antigen does not cause inoculation abscesses, and the immediate clinical results approach those obtained with the residual antigens of other organisms. In approximately two thirds of all cases of pulmonary tuberculosis, it is believed, appreciable benefit can be obtained from this antigen. The duration of improvement is at present unknown. For details, the original paper should be read.

H. J. CORPER

THE ACTION OF ULTRA-VIOLET RAYS ON THE SKIN ALBERT EIDINOW, Brit J Tuberc **22** 136, 1928

The present conception of the action of ultraviolet rays on the skin supports the theory of the production of (1) local photobiochemical substances which have bactericidal or vitamin properties, (2) local hyperemia of the skin, (3) stimulation of a leukocytic infiltration of the epidermal tissues

H J CORPER

IMMUNIZATION AGAINST CHICKENPOX K v KLSMARSZAK, Arch f Kinderh **85** 1, 1928

Immunization was effected by intracutaneous injection of 0.1 cc of citrated blood from a patient with chickenpox within thirty-six hours of appearance of the disease The duration of this immunity was not determined

SERUM REACTIONS WITH MIXTURES OF ALCOHOLIC EXTRACTS OF ORGANS AND HOG SERUM LYDIA HENNIG, Ztschr f Immunitätsforsch u exper Therap **55** 19, 1928

A large number of guinea-pigs were injected with mixtures of alcoholic extracts of guinea-pig kidney and hog serum, but it was not possible to detect antilipoid immune bodies by the Wassermann, Sach's-Georgi or Menicke reactions The animals were hypersensitive to mixtures of guinea-pig lipid and hog serum after an interval of three and one-half weeks and reacted strongly, even with lethal shock, to doses which were without effect on animals treated with extract or serum alone or on normal animals Thus the same results were obtained by use of the native lipoids as Klopstock obtained with foreign lipid preparations and interpreted as lipid anaphylaxis

JOHN HAYS BAILEY

BRESLAU INFECTION IN MICE J ORSKOV, K A JENSEN and KENJI KOBAYASHI, Ztschr f Immunitätsforsch u exper Therap **55** 34, 1928

Breslau bacilli administered orally or intravenously cause a bacteremia that is fatal Vaccination with killed organisms protected the mice, although vaccinated mice may become carriers of the infection Intracellular destruction of the organism occurs more rapidly in the vaccinated than normal mice

JOHN HAYS BAILEY

CONTAMINATION OF ISO-AGGLUTININATIVE SERUM BY BACILLI THAT PRODUCE AGGLUTININ V FRIEDENREICH, Ztschr f Immunitätsforsch u exper Therap **55** 84, 1928

The bacillus found by Thomsen to cause agglutination of human corpuscles is not agglutinative by itself, but agglutinin is present in the filtrates of broth cultures of the bacillus In contaminated serum, this agglutinin may be present side by side with alpha and beta agglutinins In 500 samples of blood, 18 instances of contamination were observed, in 11 the bacterium was isolated (in 9 bacillus "M," in 2 bacillus "J")

JOHN HAYS BAILEY

ON CHEMOSPECIFIC ANTIGEN A KLOPSTOCK and G E SELTER, Ztschr f Immunitätsforsch u exper Therap **55** 118, 1928

Diazotized serum was used as antigen The corresponding antiserum reacted by fixation and precipitation with diazotized serum from various species but most strongly as a rule with the serum of the homologous species Chemospecific antigens can be prepared in a similar way with atoxyl and serum or with atoxyl and *B proteus* X 19

JOHN HAYS BAILEY

AGGLUTINATION OF PARATHYPHOSUS B AND ENTERITIDIS BRESLAU M FISCHER and FRAULEIN GROSSMAN, Ztschr f Immunitatsforsch u exper Therap **55** 142, 1928

*Bacillus paratyphosus B* Schottmuller and *B enteritidis* Breslau may be differentiated by agglutination with their antisera in 877 and 1754 per cent sodium chloride solutions Breslau serum gives a double agglutination, while Schottmuller serum agglutinates only its antigen If the  $pH$  be varied, using physiologic solution of sodium chloride, a double agglutination is obtained with Breslau serum in all ranges, while an anti para B serum agglutinates the Breslau organisms only in the acid range

JOHN HAYS BAILEY

AGGLUTININ AND PRECIPITIN IN ANTICHOLOERA SERUM E HOEN, L TSCHERTKOW, W ZIPP, Ztschr f Immunitatsforsch u exper Therap **55** 149, 1928

The vibrios absorb the agglutinin in anticholera serum, leaving a precipitin that reacts with filtrate of cultures of the cholera vibrio This precipitin resists heating at 57 C for one hour

JOHN HAYS BAILEY

## Tumors

ANALYSIS OF 176 CASES OF CARCINOMA OF THE STOMACH SUBMITTED TO AUTOPSY M WARWICK, Ann Surg **88** 216, 1928

In 7,800 necropsies there were 570 carcinomas, of which 176 were carcinoma of the stomach The disease is more frequent in males Thirty-nine per cent occurred in the sixth decade and 29 per cent in the fifth decade, 42 per cent were in the pylorus, 37 per cent in the wall and 11 per cent in the cardia Ten per cent were diffuse, 43 per cent ulcerated, and of these 51 per cent were perforated, 16 per cent closed off and 35 per cent open, causing fatal peritonitis Obstruction was present in 34 per cent, in the great majority, at the pylorus Metastases were found in 77 per cent—liver, lymph nodes, peritoneum, omentum, lungs, mesentery, bronchial lymph nodes Emaciation was marked in 62 per cent and moderate in 20 per cent

N ENZER

A STUDY OF EPITHELIAL NEOPLASMS OF THE URINARY BLADDER KENNETH FRATER, J Urol **20** 371, 1928

The so-called benign papilloma should be classified as epithelioma of low grade malignancy With few exceptions, malignancy does not increase with recurrence The grading of a specimen removed cystoscopically can be relied on The specimen reported to be inflammatory tissue should be examined several times before exclusion of malignancy is justifiable Epithelioma of the bladder does not show variation in grade of malignancy in different parts of the same tumor

AUTHOR'S SUMMARY

SMALL CARCINOMAS OF THE PROSTATE GLAND EDWIN F HIRSCH and LOUIS E SCHMIDT, J Urol **20** 387, 1928

The results reported here emphasize again the need of a careful microscopic examination of tissues from many places of the prostate gland removed with the clinical diagnosis of benign enlargement in order that small malignant growths do not escape notice

AUTHORS' SUMMARY

ROENTGEN SARCOMA H J ALIUS, Beitr z klin chir **143** 567, 1928

Alius relates the case of a man who submitted to roentgen treatment of a lupus vulgaris for seventeen years and then developed a sarcoma on the site exposed to the rays The tumor grew rapidly and finally was excised surgically

A year later, there was a recurrence. Neither the first nor the second specimen was proved to be malignant. Four months after the second excision, the growth had recurred. Microscopic examination showed it to be a spindle cell sarcoma. A fourth recurrence was excised two months later. By the end of the month the patient complained of pains in the abdomen. The previous site of the disease was the supraclavicular region. Pain, emaciation and bloody stools followed in rapid succession. The roentgen examination with barium showed an involvement of the ascending colon. Then came dyspnea, radial paralysis of one hand and mental symptoms. Inside of three months death occurred, eighteen months after the patient first noticed a tumor. The necropsy disclosed multiple metastases in the intercostal and pectoral muscles, pleura, lungs, ileocecal lymph nodes, cecum and left temporal lobe of the brain. Admitting that the lupus had some connection with the reason for the development of the sarcoma, the author is of the opinion that the main cause was the long continued roentgen irradiation. The case is particularly interesting in that it is the only one of sarcoma following roentgen irradiation in which it was possible to follow the development of the growth histologically from its inception as an ulcer to the appearance of its malignant nature.

### Medicolegal Pathology

THE ELIMINATION OF NICOTINE IN MILK. R. A. HATCHER and H. CROSBY, *J. Pharmacol. & Exper. Therap.* **33** 1, 1927.

Characteristic physiologic responses are obtained when nicotine in as small a ratio as 1:500,000 is injected into the lymph sacs of frogs. Still smaller quantities may be recognized by the odor when concentrated and pure extracts are made alkaline. It was found that lactation was markedly lessened or altogether checked in cows and cats by nicotine, although abundant, at first, in a primipara accustomed to smoking from twenty to twenty-five cigarettes a day, the flow of milk quickly diminished. The smoking of seven cigarettes in two hours caused a marked subsidence. In purified extracts of the milk, nicotine was easily demonstrated. The effect on nurslings has not been investigated.

E. R. LE COUNT

THE LOCALIZATION OF BARBITURIC ACID COMPOUNDS IN THE BRAIN. E. KEESER and J. KEESLER, *Arch. f. exper. Path. u. Pharmacol.* **125** 251, 1927.

These investigators were unable to obtain from, or demonstrate the presence of luminal, veronal and other compounds of barbituric acid in the cerebral hemispheres, mesencephalon, cerebellum, pons or medulla, but they did find them in the thalamus and corpus striatum. These parts of the brain, therefore, should always be examined for hypnotic poisons.

The investigations, however, were undertaken because of different views which are held regarding sleep and its possible regulation by particular regions of the brain. Compounds of these barbituric acid derivatives were made with both iron and silver and recovered in their original crystalline form by chemical methods from the brains of rabbits. They were also found microscopically in the aforementioned basal ganglia by appropriate histochemical methods but not elsewhere. The conclusion by these investigators about sleep and a nerve center for its control are very reserved. They do not, for example, maintain that hypnosis due to drugs and natural sleep are necessarily brought about in the same way.

E. R. LE COUNT

CHRONIC POISONING WITH WOOD ALCOHOL. A. LEO, *Biochem. Ztschr.* **191** 423, 1927.

Experiments were made with dogs. Both synthetic methyl alcohol as well as the usual form were used, no difference was found in their action. The lethal dose for dogs is 8 cc. per kilogram. After repeated intoxications, this dose was easily borne. One dog weighing 12.5 Kg. received 1 liter of 97 per cent methyl alcohol during seven weeks. Not even a fatty liver was produced, an effect of

wood alcohol which many have regarded as quite constant. No albumin, sugar or biliary pigments appeared in the urine.

Methyl alcohol is burned to formic acid in the body, and this appears in the urine as formates. With tolerance established, the excretion of formic acid appreciably lessened. For this outcome, no entirely satisfactory explanation is given. Among those offered are the excretion of methyl alcohol unchanged, increased ability to exhale the poison or oxidize the formates, and resorption of the alcohol and its products from the urinary bladder. This lessening of the formic acid in the urine has been noted before and as a result not only of repeated poisonings with methyl alcohol, but also a consequence of poisoning with ethyl alcohol with or previous to the administration of wood alcohol.

Apparently tolerance for one confers tolerance for other alcohols. Considerable difficulty was experienced in distinguishing between the results of a true chronic poisoning and repeated acute poisonings with wood alcohol. The degree of toxicity is largely directly proportionate to the concentration. The small amount of wood alcohol in the smoke of tobacco, as tobacco is smoked in pipes, cigars, etc., is quite harmless. There is only about 42 mg. in the smoke of 70 Gm. of tobacco.

E. R. LE COUNT

FATAL EMPHYSEMATOUS GANGRENE AFTER PROBING A GRAVID UTERUS. E. M. FUSS, *Zentralbl. f. Gynak.* **52** 116, 1928.

A woman, aged 39, wore a silver, cervix-occluding pessary which a physician removed for each menstruation. On one occasion, the physician being away, the husband removed it. When the uterus was found enlarged, a few days later, a tumor was suspected. A sound was introduced, eight hours later there was a severe chill, twelve hours later, death. A short, plump, gram-positive bacillus, with the characteristics of the bacillus of emphysematous gangrene, was obtained from the blood during life and from many places after death. When the pessary was removed, a little brown fluid escaped. It is suggested that the sound carried into the uterus the anerobic bacteria from a latent infection caused by wearing the pessary.

E. R. LE COUNT

IS THE ABDERHALDEN TEST OF VALUE FOR MEDICOLEGAL PURPOSES EARLY IN PREGNANCY AND IN ABORTION? M. KERNBACH and D. BERARIU, *Ztschr. f. ges. Genschbl. Med.* **12** 487, 1928.

With the Abderhalden test, positive results may be obtained during the entire course of pregnancy, from the first weeks and for ten days after birth. The test may be positive in extra-uterine pregnancy. Positive results may be obtained after abortion, but only for about fourteen days.

### Technical

DIFFERENTIAL DIAGNOSIS OF SURGICAL FROM NONSURGICAL JAUNDICE BY LABORATORY METHODS. LUCIUS W. JOHNSON and PAUL F. DICKENS, *Am. J. M. Sc.* **176** 690, 1928.

Laboratory indications for surgical intervention are (a) persistent and increasing jaundice, with a direct immediate van den Bergh reaction, (b) dye retention, and (c) absence of bile or dye from duodenal contents. In obstructive jaundice the delay in the elimination of bromsulphalein is definite and of great value in diagnosis when taken in conjunction with the van den Bergh test. In malignant conditions of the liver it is of value in determining the amount of damage to the liver tissue.

PEARL ZEEK

THE RESORCINOL FLOCCULATION TEST FOR ACTIVITY IN TUBERCULOSIS. ADELAIDE B. BAYLIS and WARD J. MACNEAL, *Am. Rev. Tuberc.* **18** 843, 1928.

The resorcinol test is without any claim to specificity in a bacteriologic sense, but it offers some help in determining activity or arrest of the tuberculous process.

In the known tuberculous person it is a convenient and reasonably reliable method of measuring the state of activity of the tuberculous process, and it is in such cases that it would seem to have its greatest promise of usefulness. The simple test of Baylis is described, and results with its use are recorded. It obviates the use of the expensive photometer of the Vernes test. Five tenths cubic centimeter of the 1.25 per cent resorcinol solution is gently poured on to 0.5 cc of the patient's serum in a small tube, the mixture is then rapidly passed from one tube to another and back again, and the container is closed with a rubber stopper and allowed to remain in the room four hours, and in the refrigerator over night. In the morning it is again placed in the room without shaking and allowed to rest until the water of condensation has disappeared from the exterior of the tube. Reading by the naked eye is recorded as —,  $\pm$  to ++++ or atypical, according to the quantity and quality of the sediment.

H J CORPER

**DIFFERENTIAL MEDIUM FOR SALMONELLA PULICORUM, SALMONELLA GALLINARUM, PASTEURELLA AVICIDA AND ESCHERICHIA COLI** W L MALLMANN and SNYDER, *J Infect Dis* **44** 13, 1929

A dextrin-lactose agar slant medium for the differentiation of the bacteria mentioned is described.

AUTHORS SUMMARY

**THE TECHNIC OF OPERATION ON MICE** WERNER KOOSE, *Centralbl f Bakteriol* **106** 140, 1928

This article describes and illustrates certain procedures and operative methods of value in various operations on mice, such as preliminary and postoperative care, types of narcosis, technics for castration, suprarenalectomy, decerebration, etc.

PAUL R CANNON

**CREATININE ESTIMATIONS OF THE BLOOD (ONE THOUSAND ANALYSES)** F LICKINT, *Klin Wchnschr* **7** 2341, 1928

Creatinine increases fairly regularly with the total nonprotein nitrogen, but unexplained individual deviations from this do not permit the substitution of the complicated nonprotein nitrogen determinations by the simpler creatinine estimations.

AUTHOR'S SUMMARY

**SIMPLIFICATION OF THE HOHN CULTURAL DEMONSTRATION OF B TUBERCULOSIS** F E LOEWY, *Munchen med Wchnschr* **75** 2096, 1928

Thick-walled centrifuge tubes (12 cc) are provided with several small glass beads, stoppered with a cork and sterilized dry. About 1 to 1.5 cc of sputum is transferred into the tube which is then filled with 10 per cent by volume of sulphuric acid, stoppered, vigorously shaken, placed horizontally for twenty minutes and centrifugated. Two tubes of egg medium are inoculated with the sediment and are examined from time to time after two weeks by stained preparations.

EDWIN F HIRSCH

**THE PROGNOSTIC VALUE OF INDICAN IN THE BLOOD SERUM IN NEPHRITIS** A KROKIEWICZ, *Virchows Arch f path Anat* **266** 239, 1927

The author found increased indican in the serum, a more reliable diagnostic and prognostic test in nephritis than an increase in nonprotein nitrogen or in other substances. The Jolles-Haas test for indican was found to be simple and reliable, and its use is recommended in all cases of nephritis. The test was negative in fifteen patients with acute nephritis, all of whom recovered without uremia. In twenty-five cases of chronic nephritis, uremia developed in nine patients with positive indican tests but was absent in sixteen with negative tests.

B R LOVETT



# Society Transactions

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## PHILADELPHIA PATHOLOGICAL SOCIETY

*Regular Meeting, Nov 8, 1928*

J HAROLD AUSTIN, M D, *Presiding*

### THE RÔLE OF ALLERGY IN TUBERCULOSIS (ABSTRACT OF ANNUAL GROSS LECTURE) ARNOLD R RICH

The lecture was concerned with the precise definition of bacterial allergy, and the role which this phenomenon plays during the course of tuberculous infection

In the discussion of the character of the local allergic tissue reaction, it was pointed out that accelerated tubercle formation should not be regarded as a form of the allergic reaction, and that any local fixation of bacilli which may occur in the immune body is more probably a result of specific precipitation than of the inflammation of allergy

Tissue culture experiments demonstrating that allergy consists in a cellular change were described. It was shown that no plasma antibody is necessary for the injury and death of allergic cells exposed to tuberculoprotein

Principles established by experiment concerning the interrelation of allergy, dosage, virulence and resistance were discussed, it was shown how the application of such principles enables one to interpret more accurately the pathogenesis of lesions observed at autopsy. The lesions characteristic of acute caseating miliary tuberculosis and of tuberculous meningitis were used as examples. In the discussion of the latter lesion it was pointed out that tuberculous meningitis cannot be produced by direct blood stream infection of the meninges, but that it depends on the establishment of local caseous foci from which bacilli may be discharged directly into the meninges or the ventricular cavities

The relation of allergy to acquired resistance was discussed, and evidence was presented against the current view that allergy is the mechanism of acquired resistance. This evidence, while by no means conclusive, is sufficient to warrant a thorough inquiry into the question as to whether allergy is necessary for the operation of immunity in tuberculosis. Up to the present time, no one has proved that it is necessary in tuberculosis, even though it may be of service in other infections in which the blood plasma possesses demonstrable bactericidal or lytic properties, or the phagocytes marked bactericidal powers. If allergy is not necessary for immunity, procedures directed toward desensitization might be of considerable value in certain cases, for the necrotizing activity of allergy is well known to be responsible for the greater part of the tissue destruction observed in tuberculosis. Clinical evidence was cited indicating that treatment with tuberculin is effective especially in the instances in which desensitization is produced. Tuberculin therapy carried out from the standpoint that desensitization permits repair by restoring the tissues to their normal indifference to tuberculoprotein, and so preventing necrosis of encapsulating granulation tissue, is different in theory and method from that carried out from the standpoint that the production of focal inflammatory reactions about lesions promotes their healing. It is urgent to determine by experiment whether or not allergy can be abolished while resistance remains intact. There is evidence that it can be, but further work is necessary to settle the question in tuberculosis as well as in all other infections. Experiments in progress indicate that a high degree of acquired immunity can be demonstrated in the absence of allergy in certain other infections

Acquired immunity in tuberculosis may depend on factors similar to those operating in natural immunity rather than on a specific bactericidal mechanism. Certain characteristics of natural immunity were discussed, but further work is necessary for the understanding of just what it is that inhibits free parasitism in natural immunity. The theory that natural immunity is a result of a rapid and vigorous cellular attack on the invading micro-organism is untenable

## NEW YORK PATHOLOGICAL SOCIETY

*Regular Meeting, Dec 13, 1928*HARRISON S. MARTLAND, *President, in the Chair*

## FATAL FAT EMBOLISM B. M. VANCE

Fat embolism is the name given to the condition which occurs when globules of liquid oil appear in the circulating blood and lodge in the smaller vessels and capillaries throughout the body. The effect of this process on the system depends on the number and distribution of the emboli. In most instances they are few, and little disturbance takes place. In the occasional case, however, many may be present, and serious and even fatal complications follow their appearance.

Almost all fatal cases of fat embolism are the result of injuries involving fatty tissues, such as fractures of the shafts of the long bones, severe injuries to the subcutaneous fat, or orthopedic manipulations of the lower extremities. Traumas of this sort may set free much liquid fat from the cell envelopes and rupture many small venules in the immediate vicinity, so that a large amount of oil may be aspirated into the venous circulation. Immediately after this, fat emboli appear in the pulmonary vessels.

Grondahl (*Deutsche Zeitschr. f. Chir.* **111** 56, 1911) described two clinical varieties of fat embolism.

1 The first type is known as pulmonary fat embolism and is found in persons whose cardiac musculature is weak. The emboli appear in large numbers in the pulmonary arterioles and capillaries and interfere with the passage of the blood through the lungs. The right ventricle of the heart is not strong enough to force the oily plugs onward into the systemic circulation, and the patient, after an interval of several hours during which he is free of untoward symptoms, dies of acute asphyxia and cardiac collapse.

The following case is a good example of this condition.

CASE 1—A white man, aged 62, sustained fractures of the right femur, right tibia and right fibula in an automobile accident. He survived for thirty-six hours, dying in a severe asthmatic attack with definite signs of pulmonary edema.

The necropsy disclosed large edematous lungs which, on microscopic examination with osmic acid and sudan III, revealed numerous fat emboli in the pulmonary vessels and capillaries (fig. 1). A few others were found in the myocardium, kidneys and brain, but were of slight consequence. In addition, a moderately enlarged heart, an appreciable coronary arteriosclerosis, chronic interstitial nephritis, hydronephrosis, hypertrophy of the prostate and senile atrophy of the brain were present. It was evident from the examination that the oil globules in the blood vessels of the lungs had overtaken a heart already weakened by a chronic cardiorenal condition.

2 The second type is found usually in those persons whose right ventricles are strong enough to drive the fat from the pulmonary vessels into the general circulation. The emboli are carried to the different organs of the body in large numbers. As many of these invaders reach the brain and evoke characteristic symptoms, this variety is known as cerebral fat embolism.

Clinically, these cases show an interval of from thirty to forty-eight hours after the injury that is free from noteworthy symptoms except slight restlessness and dyspnea. The patient then lapses gradually into coma, which becomes deeper and deeper until death occurs several days later.

Contemporary with the onset of the coma, the skin of the upper part of the chest, the shoulders and the front part of the neck shows numerous petechial hemorrhages which tend to gather into small groups of six or seven. Grondahl declared that these lesions are the result of fat emboli lodging in the skin.

The following three cases are typical.

CASE 2—A white man, aged 25, was injured in an automobile accident, fracturing the shaft of the right femur. Thirty hours later, he lapsed into coma in which he remained until his death five days later. Numerous petechial hemorrhages were present in the skin of the chest.

CASE 3—A white woman, aged 45, sustained an extensive fracture of the right tibia and fibula in an automobile accident. There was a gradual lapse into coma two days later, and she remained in this state until she died four days after the injury. Petechial hemorrhages were also noted in the skin of the upper part of the chest.

CASE 4—A white woman, aged 47, incurred fractures of both clavicles and a few ribs and, in addition, an extensive injury to the subcutaneous fat about the

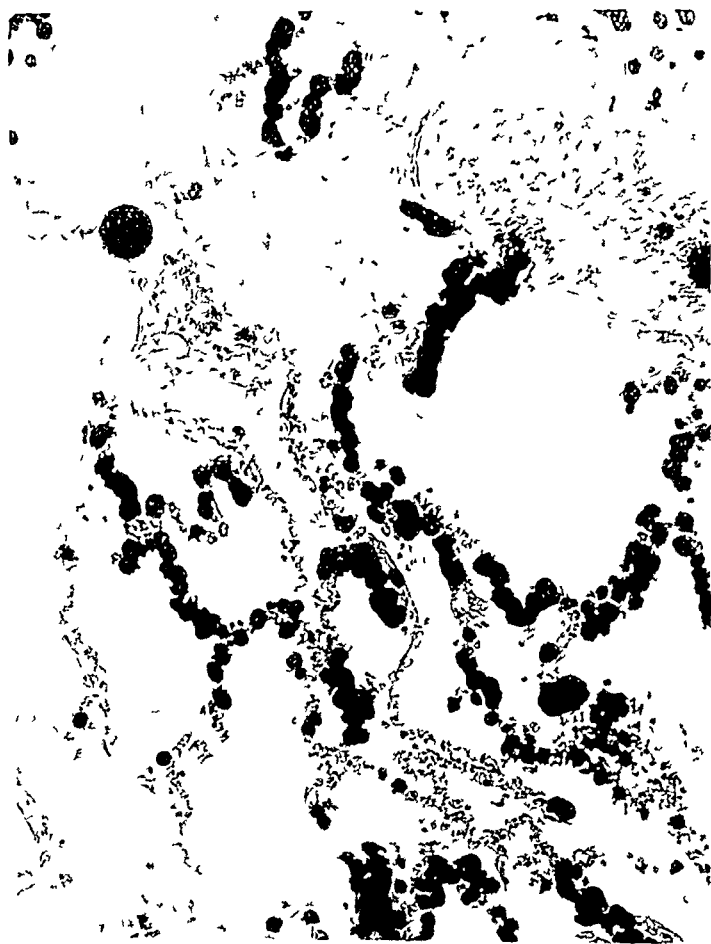


Fig 1 (case 1) —Fat emboli in the pulmonary capillaries. Osmic acid stain.

left knee in an automobile accident. Aside from the notation that she died in coma four days after the trauma, a clinical history was not obtained.

All three cases, however, showed practically similar lesions at necropsy.

The lungs were congested and edematous. In all, a slight peribronchial pneumonia was present. Minute hemorrhagic infarcts were noted in case 3. Fat emboli were demonstrated in the smaller arterioles in large numbers, but were not as evident in the capillary network.

Parenchymatous organs like the liver and kidneys did not show definite pathologic changes, though fat emboli could be demonstrated readily enough by microscopic examination. In the kidneys they appeared as characteristic pretzel-like coils in the glomerular tufts (fig 2).



Fig 2 (case 4) —Fat emboli in glomeruli of kidney Sudan III stain



Fig 3 (case 4) —Petechial hemorrhages in brain caused by fat emboli

On macroscopic examination, the heart muscle was permeated by small streaky hemorrhages, from 2 to 4 mm in diameter. Microscopic examination disclosed that the small arterioles in such areas were plugged with a sausage-shaped oil globule. The muscle fibers immediately adjacent were atrophic, filled with small fatty granules and surrounded by red blood cells. The lesion caused by the embolus had all the characteristics of a minute hemorrhagic infarct.

The brain showed numerous petechial hemorrhages, quite prevalent in the white matter, but infrequently found in the gray matter (fig 3). Fat emboli were discovered in the small arterioles in the midst of the hemorrhagic areas, while around the vessel was a zone of necrosis in which were grouped red blood cells and a few lymphocytes and leukocytes, mixed in with a collection of large ovoid cells, presumably of glial origin (fig 4). The lesion was undoubtedly a minute infarct caused by the fat embolus.

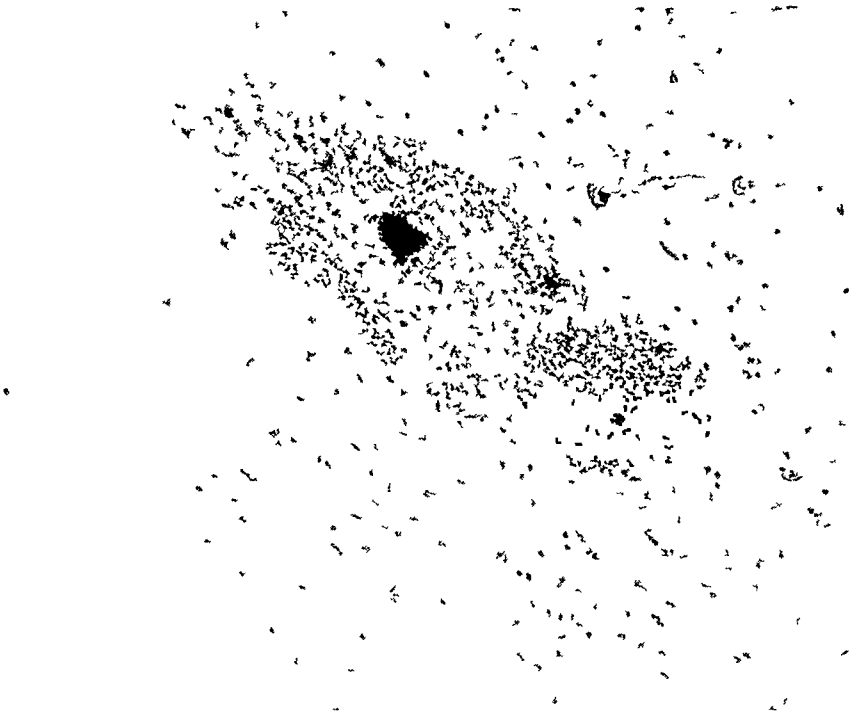


Fig 4 (case 4) —Lesion produced by a fat embolus in an arteriole of the brain. Osmic acid stain.

Apparently the liquid fat, after passing into the systemic circulation, literally bombarded the brain in the form of thousands of minute emboli. This in itself is sufficient to explain the rather dramatic lapse into coma which later ended in death.

#### DISCUSSION

HARRISON S. MARTLAND. I have been very much interested in fat embolism for many years and did not believe until recently that it was a serious lesion. Roswell Park in 1884 was the first American surgeon to call attention to the danger of fat embolism after traumatism to the long bones. During the war, Bissell, of the Mayo Clinic, again called attention to the fatal outcome in some cases of fat embolism. He claimed that he could often suspect fat embolism by the gross appearance of the organs at autopsy. He advised a special autopsy technic for opening the right side of the heart and the lungs to avoid contamination. In a few patients with clinical pictures of so-called surgical shock dying after operative procedures on bones, amputation of the breast for cancer and the surgical cure

of umbilical hernia in the obese, he found fat globules in the blood of the right side of the heart and an extreme bloody engorgement of the lungs, which blood showed oil droplets. During the war, Dr. Robertson and myself in Paris, did not give great credence to the seriousness of fat embolism. Since this time there has been considerable discussion as to how important it is as a cause of death. In some of my recent work on traumatic cerebral hemorrhages of the multiple, punctate variety (ring hemorrhages which I have attributed to concussion), I mentioned the fact that it was almost impossible at times to know whether fat embolism did not play an important etiologic factor in these cases. In the development of the "Punch drunk" theory the same question came up, so I am greatly interested in Dr. Vance's demonstration. I would like to know how often in his medicolegal work he is able to attribute death to fat embolism, whether he recognizes it grossly, and whether in systemic fat embolism he has noted the patency of the foramen ovale.

Askanazy has reported multiple punctate hemorrhages in the white matter of the brain following a simple fracture of the femur in which he found a patent foramen ovale. He thought systemic fat embolism was much more apt to occur when the foramen was open, as otherwise the lungs filtered out most of the fat. The frequent occurrence of the lesions in the white matter and deeper portions of the brain and their absence or scarcity in the gray cortex may also be explained on mechanical grounds, as fat droplets will more readily enter the central ganglionic system of vessels than the cortical, and when they enter the cortical vessels are much more apt to lodge in the long medullary arteries of the cortical system which supply the centrum ovale. According to Bissell, fat entering the venous circulation markedly increases the viscosity of the venous blood and results in a rise in venous pressure and a fall in systolic, hence the resemblance to surgical shock.

JAMES EWING. As far as I know, it is a long time since any definite additional knowledge has been thrown on the pathology of fat embolism. Therefore, I feel one can congratulate Dr. Vance on having subdivided cases into those in which the main disturbance is in the pulmonary circulation and others in which it must be in the systemic circulation, particularly in the brain. That is, I believe, a new point of view, and a definitely new contribution. I would raise the question whether in addition to the weakness of the heart the quantity of fat concerned in the embolism might not have an important bearing on the course of the case. I have had the opportunity to examine a group of animals in which oil had been injected into the circulation, in these the main lesion was in the lungs, fat could be found in the lungs in great quantity, and death was by asphyxia. I think the cardiac power was presumed to be normal here, and I simply raise the question whether the quantity of fat may have something to do with the fate of the case as well as the character of the circulation, yet I am quite prepared to accept Dr. Vance's explanation as to the activity of the power of the right ventricle.

B. M. VANCE. I think cases of fat embolism which have a fatal termination are rare. Less than ten have been noted among our Medical Examiners' cases of the past ten years.

In my series of cases an obviously open foramen ovale was not present but was either closed or open by such a small slit that it was improbable that much liquid fat was forced through this opening. It is my own opinion that in the cases of cerebral fat embolism most of the emboli were forced through the pulmonary capillaries into the systemic circulation.

The point raised by Dr. Ewing is interesting. The amount of liquid set free around the site of a recent fracture probably amounts to about 4 ounces of fat mixed with blood. I think in the majority of instances that the human organism is not seriously embarrassed by the fat immediately absorbed into the pulmonary circulation from the site of such an injury. The absorption is usually gradual, and if the torn venules in the injured area close rapidly, the absorption will cease. It is only rarely that an amount of liquid fat at all comparable to the amount of oil injected into the veins of experimental animals enters the pulmonary capillaries of the human patient. When this does occur, death takes place just as rapidly.

## METASTASIZING ADENOMA OF THE THYROID FREDERICK H MCKILL

There is a definite group of epithelial tumors of the thyroid gland which present a benign histologic picture and run a relatively benign course. They metastasize to bone characteristically, but the route of metastasis and the duration of the secondary tumors differ from the other malignant epithelial tumors of the thyroid. Connheim, in 1876, was the first to separate this type.

Mrs G M, aged 45, entered St Luke's Hospital, Nov 23, 1922, because she suddenly vomited a pint of bright blood. She had had a goiter for many years but enjoyed good health until four years before admission, when she began to have moderate dyspnea on exertion. Physical examination revealed a large, irregular thyroid gland and dulness to percussion for 8 cm below the manubrium sterni. Roentgen examination showed increased density in the upper mediastinum, dilatation of the entire esophagus and displacement of the trachea to the right.

Five years later the patient was readmitted to the hospital complaining of a painful lump beneath the right breast, which had been present for at least three years. At this time a growth in the rectum was found which proved to be a squamous type of epithelioma. She died six months later, emaciated, cachectic, dyspneic, and suffering constant pain because of chronic obstruction from the rectal tumor.

At autopsy the thyroid gland was irregularly enlarged and firmly adherent to the anterior and lateral aspects of the trachea, and its base was adherent to the aortic arch. A thick fibrous capsule enveloped the gland. The greater part of the cut surface was smooth, pale brown and translucent, with scattered hemorrhagic and calcified areas. A circumscribed nodule, 4.6 cm in diameter, was situated in the upper right lobe. Its surface was tan, opaque, of velvety smoothness and separated into lobules. The fifth right rib was the site of an ovoid tumor measuring 10 by 5 by 4 cm. It was situated 7 cm from the costochondral junction and completely replaced bony tissue. On section, the surface was tan-colored and smooth, its appearance being identical with the tumor in the apex of the thyroid gland. Other metastases were not discovered.

Sections from the colloid goiter showed atrophy and degeneration. The alveoli were decreased in number and lined with low cuboidal epithelium. Many were dilated and contained eosinophilic colloid. A few of them had colloid which took a basophilic stain. The stroma was greatly degenerated, the collagen being hyalinized and the nuclei absent.

The tumor in the apex of the thyroid gland consisted of a small-cell adenoma of the fetal type. The central portion contained mature alveoli, while peripherally the epithelium was arranged in columns, some of which had a lumen, while others did not show any attempt toward lumen formation. The epithelium was embryonal in type, with small nuclei rich in chromatin and scanty cytoplasm which stained deeply with eosin. There was colloid formation in a small number of vesicles. The stroma was delicate and contained few blood vessels.

Sections through the tumor from the rib showed columns of embryonal epithelium which were more differentiated than in the primary nodule in the thyroid in that the nuclei were vesicular and paler. They also showed a more pronounced tendency to form alveoli, and most of them contained eosinophilic colloid. Many of the alveoli were round, some were oval and elongated. The stroma was delicate but more abundant than in the original tumor, and it carried many more blood vessels with it.

## MUSCLE LESIONS ENCOUNTERED IN EXPERIMENTAL SCURVY GILBERT DALLDORF

This report is concerned with a striking lesion observed in the intercostal muscle of guinea-pigs. The animals were the subject of feeding experiments conducted by Dr Walter Eddy at Teachers' College. Dr Eddy was studying scurvy and had found that weight curves and gross appearances were often too indefinite to justify a diagnosis. In such cases, the animals were examined histologically.

The anatomic manifestations in experimental scurvy are well known and have been precisely described by many writers. When the established criteria for the

diagnosis of scurvy were employed, there was seldom difficulty in determining the presence or absence of the scorbutic process in the animals of this series, even when it was early or only partially developed. The changes at the junction of bone and cartilage in the ribs proved to be representative of the bone lesions of scurvy and technically simple to handle, hence, liberal samples were therefore taken from these areas.

Fifty guinea-pigs were used, ten of which were normal. The remaining forty were scorbutic, and the lesion to be demonstrated was found in twelve of these.

Scattered through the intercostal muscles were muscle fibers which had ruptured, often into several fragments. Such fragments were frequently surrounded by large endothelial giant cells. Layers of fibroblasts formed along the ruptured muscle cells, proliferating until they frequently formed a mass greater than the muscle itself. In addition, in some cases, large cells with acidophilic cytoplasm were found, frequently in process of mitotic division. These looked like muscle cells, and in some fields their activity was so great as to simulate a muscle cell sarcoma.

In other cases, the muscle cell proliferation was not present. The muscle remnants lay as hyalinized fragments in a matrix of lax connective tissue, poor in collagen.

The lesion varied greatly in extent. In some cases most of the intercostal muscles were involved, in others, only a few focal lesions were found.

It seemed impossible that the experienced and careful workers who had previously studied the disease might have missed such obvious lesions if they examined the muscles. It is true that most studies have been centered on the bony changes which have been considered the essential lesion. However, scarring in the muscles has frequently been described in chronic scurvy and has been considered secondary to changes in the bone.

The lesion described in this report occurred in early, acute scurvy, but the facts which suggest that it may be associated with the scorbutic process are:

- 1 The changes are found only in scorbutic guinea-pigs, although normal animals have been carefully searched.

- 2 The changes always appear in pigs in which the bone lesions are in an early stage of development.

- 3 They have many histologic features in common with the bone lesions with which they coincide.

- 4 They bear the same relationship to the muscle lesion found in chronic scurvy that the acute bone lesion bears to the bone lesion in chronic scurvy.

#### DISCUSSION

JAMES EWING. Dr Dalldorf's slides were extremely interesting and surprising to me. I at first doubted whether they had anything to do with the scorbutic process, but the lesions occurred in such a high proportion of animals, and the control material was so adequate that I think we are justified in assuming that they are a part of the scorbutic process. The remarkable character of the lesion is interesting to the histologist, it suggests the extremely powerful influence of nutrition on the tissues. I think that the process in the muscle mainly concerns the muscle cells, and I could not convince myself that there was any participation of fibroblasts. I do not know of any parallel to such a process in the range of pathology.

HARRISON S. MARLAND. It has occurred to me that in several metabolic diseases and a few of obscure infectious or toxic (?) origin there are circumscribed, possibly inflammatory, lesions in the subcutaneous tissues and muscles—the so-called fibrositis in chronic focal infections, nodes over the sacroiliac joints in gout, etc. Little serious study has been given these lesions from a histologic standpoint. In fact, we do not know very much about any of them. I am wondering if these muscle lesions in scurvy are not somewhat parallel, and have escaped notice clinically in human scurvy.



## Book Reviews

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TUMORS ARISING FROM THE BLOOD VESSELS OF THE BRAIN ANGIOMATOUS MALFORMATIONS AND HEMANGIOBLASTOMAS By HARVEY CUSHING and PERCIVAL BAILEY Price, \$7.50 Pp 219, with 159 illustrations Springfield, Ill., and Baltimore Charles C Thomas, 1928

This is a monograph based on the systematic, clinical and anatomic studies of neurosurgical cases by the authors. There are two parts: one dealing with angiomatous malformations with fourteen illustrative cases and the other, the hemangioblastomas with ten cases. Each part has an exhaustive bibliography in which bracketed numbers indicate the pages in the text in which the work in question is discussed. The presentation is comprehensive, balanced, orderly and well illustrated. The publisher has done his part excellently. The summary gives the principal outcome so well that it is repeated here. "Blood vessel 'Tumors' of the brain may be divided into two major groups: (1) the angiomatous malformations and (2) the angioblastomas or true neoplasms of blood vessel elements. The angiomatous malformations are undoubtedly attributable to some fault of development, and they may be clearly distinguished from the blood vessel tumors proper by the fact that traces of compressed nervous tissue are invariably present between the vascular loops comprising the lesion. (1) The angiomatous malformations may be chiefly capillary (telangiectatic), chiefly venous (angioma venosum) or arteriovenous (angioma arteriale) in their composition. They more commonly occur in the cerebral hemispheres and are often provocative of epileptiform attacks, frequently Jacksonian in character. Only occasionally are these lesions found in the hind brain. Both the venous and the arteriovenous malformations are primarily surface lesions of the hemisphere, and three types may be recognized: a simple enlargement of a single vessel, a tangled enlargement of one or more vessels, or a more complicated (racemose) type in which the lesion extends from the cerebral surface like an inverted cone with its apex abutting on the ventricle into which a terminal hemorrhage not infrequently occurs. The venous angiomas, unless they are associated with trigeminal naevi, are not likely to be diagnosed until they are unexpectedly exposed at operation or autopsy. The arterial angiomas, on the other hand, may often be recognized by an audible bruit as well as by secondary effects of the aneurysmal (arteriovenous) communications which lead to enlargement of the extracranial vessels, of the carotids, or even of the heart. Whereas the venous angiomas are unaccompanied by a choked disc, the aneurysmal lesions are apt to be, and a unilateral exophthalmos is not infrequently produced. The treatment of any of these angiomatous malformations by surgical or other procedures, unless possibly by radiation, is unsatisfactory. (2) The angioblastomas are true tumors composed of angioblastic elements. They are rarely if ever accompanied by facial naevi, but that some of them at least, if not all, possibly have a congenital anlage must be acknowledged in view of the fact that the lesions may be multiple. Their favored, if not their exclusive, site is in the cerebellum where they are often median tumors that appear to arise from a region near the posterior end of the fourth ventricle. They may be largely cystic or largely solid lesions. Histologically, they are conveniently divided into those predominantly capillary, those predominantly cellular, and those predominantly cavernous. It is rare, however, to find any tumor of pure type for they differ in degree rather than in kind. They have often been mistaken for vascular gliomas or meningiomas but they invariably show, when properly stained, a network of reticulum which serves to distinguish them from other growths. Some of the cerebellar hemangioblastomas are associated with a similar lesion in the retina (one case in our series of eleven), angiomas of the spinal cord, cystic kidneys, cysts of the pancreas, hypernephromas and other lesions. This represents a new disease which has familial tendencies

and should be known as Lindau's disease from its principal discoverer. The cerebellar hemangioblastomas like any other cerebellar tumors, should be treated, when possible by extirpation. Apart from the unusual vascularity of some of the lesions, they offer no unusual surgical difficulties. When cystic tumors are encountered, care should be taken to remove the mural nodule of the tumor for otherwise a recurrence of symptoms, due either to refilling of the cyst or to progressive enlargement of the tumor, may be expected."

AMERICAN TYPE CULTURE COLLECTION. CATALOGUE OF CULTURES. Ed 2  
(Distributed without charge) Pp 142. Chicago. The John McCormick  
Institute for Infectious Diseases, 1928

Some evidence of the vitality of the American Type Culture Collection is given by this second edition of its catalogue, as a revision of its list of cultures has been made necessary by a considerable change in the content of the collection. During the past four years, the collection has grown from 750 to 2,000 cultures. Since the publication of the first catalogue, two years ago, 130 cultures have been discarded as impure, atypical or lost, and 650 cultures have been acquired. Of the 2,000 cultures listed in this edition, 1,100 are bacteria, 600 fungi and 300 yeasts. The private collections of Prof F W Tanner, Prof I C Hall and Dr S A Waksman are still available through the generosity of the owners. In a similar manner, Dr C B Sherbakoff, of the University of Tennessee Agricultural Experiment Station, has placed his large collection of *Fusaria* at the disposal of the curator.

The organisms are listed in alphabetical order under the names used in Bergey's Manual of Determinative Bacteriology as far as that system of nomenclature is applicable. The editors of the catalogue hope that the "liberal use of cross-references will facilitate the finding of organisms which are listed under unfamiliar names." Short of the publication of a complete synonymy, which would be unnecessarily expensive and laborious, these cross-references are certain to appear to be inadequate. An example of a puzzle to be worked out among these names is the problem before the medical bacteriologist who wishes to find the list of cultures of the "Friedländer bacillus." This familiar organism appears under the title of "Klebsiella," cross-reference "*Bacterium mucosus capsulatus*." A closely related organism, listed in a cross-reference as "*Bacillus lactis aerogenes*" (not Bacterium) appears under the caption of "*Aerobacter aerogenes*." These seem to be inconsistencies and artificial separations. The nomenclature, however, is a workable one from the point of view of the cataloguer. This is not the place for any extended comments on bacteriologic nomenclature or for the expression of an inadequate opinion on uncertainties of the taxonomy of this branch of biology. It will be interesting, however, to observe what effect the use of the names chosen in this catalogue will have on the fixation and general use of the nomenclature set forth in Bergey's Manual.

Additional evidence of the service which this culture collection is rendering bacteriologists was given at the meeting of the Society of American Bacteriologists in Richmond in December, 1928, in a report from which Dr L A Rogers has permitted the reviewer to make excerpts. During the past four years there has been a steady increase in the number of cultures supplied to bacteriologists. Since 1925, 12,913 cultures have been sent out in response to 2,553 orders for them. During the year 1928, 1,022 orders were received, and 4,761 cultures were sent out. Most of the cultures have been furnished for teaching purposes. Many, however, have been used for investigations. Of the total, 4,178 have been sent to institutions, 156 to individuals and 427 to commercial dealers in biologic supplies.

The staff of those engaged in the care of this collection has been increased by the appointment of Mr W R Albus, as bacteriologist.

Although the Culture Collection has been of great immediate service to bacteriologists and, by the preservation of type strains, promises aid of inestimable value to investigators and other students in the future, it is faced by the problem of its own perpetuation. This is almost exclusively a financial problem. In 1929, the agreement of the General Education Board to contribute to the support of the

collection will have completed its fifth and final year. When the agreement was entered into, it was understood that an earnest effort would be made to put the collection on a self-sustaining basis. This effort has been made, but the collection is not self-supporting.

The administration has been economical, and no expense has been incurred for rent of quarters. Nevertheless, until 1928, income from the sale of cultures did not meet half of the expenses, and it is apparent that it will not be possible to maintain the collection in its present condition without assistance from other sources. It is also obvious that enlargement of the collection will be required to meet the increasing needs of bacteriologists. Those who have been in closest touch with the collection hope to see it increased, housed in an adequate building which would provide separate floors for bacterial and fungous cultures, and laboratories for special research, under the care of a larger staff of bacteriologists and mycologists. It would be a great misfortune if the collection were to be distributed on account of lack of financial support. Maintenance of the collection on a small scale would be less unfortunate, but would undesirably restrict its service. On the other hand, it would be greatly to the advantage of all interested in bacteriology if sufficient endowment could be secured to permit the collection to fulfil all its functions.

The curators of the collection again urge those who describe new species or make studies of older ones to send to the collection cultures, reports and references to their work. Contributions of this sort add new life and value to the collection.

GREEN'S MANUAL OF PATHOLOGY AND MORBID ANATOMY. Fourteenth edition. Revised and enlarged by A. PINEY, M.D., M.R.C.P. Pp. 650, with 261 figures and 7 colored plates. Philadelphia: Lea & Febiger, 1928.

Since the preparation of the thirteenth edition of the deservedly popular Green's Manual by Bosanquet and Wilson, Dr. Thomas Henry Green has died, but Dr. Piney, who has prepared the fourteenth edition, pays tribute to the continuing influence of the author. Dr. Piney has revised the sections on nephritis and surgical shock, and has made minor corrections and additions. There are numerous new illustrations, but none of the older ones has been replaced, which may be regarded as unfortunate because many are merely diagrammatic. The general character of the book remains unchanged. There are 416 pages of text devoted to general pathology and 219 to diseases of special tissues and organs. Of the part on general pathology, 86 pages are devoted to parasites, animal and vegetable, and 27 to immunity. The subject matter covered is extensive, but this description of the make-up of the book serves to indicate the brevity and conciseness of the presentation. It must also be remarked that extreme clarity prevails.

There comes a time in the life history of a scientific textbook or manual when simpler forms of revision are inadequate for the presentation of the progress recorded within its special field. A manual, such as Green's, is by its very nature principally for the use of students of medicine or related subjects. The introductory statement reads "The Art of Medicine must obviously be based upon a knowledge of the nature and the causation of disease, and it is this information that pathology attempts to supply." This objective, however, cannot be attained unless pathology is regarded as a living science, enlarging its observations, clarifying its hypotheses, broadening its experimental demonstrations and correlating its old and new facts. It is not nationalistic and cannot be covered by references almost solely to publications in the English language. Parasitology and immunology have become so extensive that their brief presentation in a book on pathology must of necessity be incomplete. Modern immunology draws on physical chemistry for its explanations and discards the Ehrlich diagrammatic and inaccurate hypotheses. The physiology of valvular defects of the heart is as deserving of discussion as that of nephritis. Subacute bacterial endocarditis is certainly of great clinical and pathologic significance. Rheumatic fever in relation to the heart and blood vessels should not be dismissed with two sentences. If endometrioma is

found in 30 per cent of gynecologic cases in which operation has been performed, it deserves consideration. Too great value is to be ascribed to the investigations of the Spanish school on the interstitial tissues of the central nervous system to have it neglected entirely. Metaplasia is not limited to epithelial cells. In spite of an "erratum" note concerning vitamin D in connection with rickets, the general discussion of vitamins should involve more than a consideration of vitamins A, B and C. There can be no satisfactory compromise between the older and newer views of nephritis. If shock is to be discussed, anaphylactic and allergic manifestations are too important in man to be omitted. These observations must make it apparent that a modest revision, singly or in series, cannot serve to modernize a book however excellent it was in its day and generation. Medicine is on wings, and he who would be with her and of her must fly to keep the pace. The author of a book which is to represent the scientific background of medicine must recognize these established advances.

**ORGANIC LABORATORY METHODS** By the Late PROFESSOR LASSAR-COHN. An authorized translation from the general part of the fifth revised edition, by RALPH E. OESPER. Edited by ROGER ADAMS and HANS T. CLARKE (No 2 of the World Wide Chemical Series, edited by E. EMMET REID). Price, \$6.50. Pp. 469. Baltimore: Williams & Wilkins Company, 1928.

This translation of the general part of Professor Lassar-Cohn's well known book deals with the laboratory technic of organic chemistry. It contains a great deal of useful information concerning the basic principles of such fundamental procedures as distillation, crystallization, filtration and extraction. Its limitations for the worker in the biologic sciences are indicated in the translator's preface in which the aim of the book is described as being "to cite and outline the methods by which typical difficulties have been overcome and leave the adaptations of the suggestions to the problem at hand to the resourcefulness of the reader." The most serious defect of the book, from the standpoint of the biologist who wishes to apply the technic of organic chemistry to the specific needs of his own problems, is indicated by the fact that most of its many references are to papers written before 1900. There is thus no reference to such familiar methods as the use of collodion membranes in dialysis, or to the use of pyrex glassware, or electrical appliances of all kinds such as motors, drying ovens and hot plates. The book will appeal, therefore, to those interested in the broader aspects of the subject rather than to those interested in knowing whether methods exist which may be applied to the solution of the specific problem at hand.

**WILLIAM HARVEY** By ARCHIBALD MALLOCH, Librarian, New York Academy of Medicine. Price, \$1.50. Pp. 103, with 10 full-page plates and 3 text illustrations. New York: Paul B. Hoeber, 1929.

This little book is the outgrowth of an address to commemorate the publication of Harvey's great book in 1628. It is a reprint, with corrections, from the *American Journal of Surgery*, September and October, 1928. Thoroughly familiar with the sources of information, Dr Malloch sketches briefly the various phases of Harvey's life, with particular reference to the discovery that the blood moves in a circle. But no side of Harvey's activities or relations appears to have been neglected and the sketch, though brief, is unexpectedly comprehensive. Harvey's observations on the color of the lungs of the new-born and its significance are quoted. Pathologists may be interested in reading what Harvey, who was an experienced morbid anatomist, said on that point, namely that lungs of fetuses having breathed "put on a white colour, and by this observation of the different complexion you may discover whether a mother brought her child alive or dead into the world, for instantly after inspiration the lungs change colour, which colour remains, though the foetus die immediately afterwards." Medical students, physicians and all who have any interest in the history of science and the lives of its leaders, will be grateful for Malloch's account of the life and work of Harvey.

## Books Received

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GREEN'S MANUAL OF PATHOLOGY AND MORBID ANATOMY Revised and enlarged by A Piney, M D, M R C P, Research Pathologist, Cancer Hospital, London Fourteenth edition Cloth Price, \$7 50 Pp 650, with 269 illustrations Philadelphia Lea & Febiger, 1928

MICROBIOLOGY MONOGRAPHS, GENERAL, AGRICULTURAL, INDUSTRIAL Edited by R E Buchanan, Iowa State College, E B Fred, University of Wisconsin, and S A Waksman, Rutgers University Volume I Morphologic Variation and the Rate of Growth of Bacteria By Arthur T Henrici, M D, Professor of Bacteriology, the University of Minnesota Price, \$3 Pp 194 Springfield, Ill Charles C Thomas, 1928

RECENT ADVANCES IN BACTERIOLOGY AND THE STUDY OF THE INFECTIONS By J Henry Dible, M D (Glasgow), M R C P, Professor of Pathology and Bacteriology in the Welsh National Medical School Price, \$3 50 Pp 363, with 22 illustrations Philadelphia P Blakiston's Son & Company, 1929

WILLIAM HARVEY By Archibald Malloch, M D (McGill), M R C P (London), Librarian, New York Academy of Medicine Price, \$1 50 Pp 103, with 13 illustrations New York Paul B Hoeber, 1929

HISTORY OF MEDICINE With Medical Chronology, Suggestions for Study and Bibliographic Data By Fielding H Garrison, M D, Lieut-Col, Medical Corps, U S Army, Surgeon-General's Office, Washington, D C Fourth edition, revised and enlarged Cloth Price, \$12 Pp 996, with 286 illustrations Philadelphia W B Saunders Company, 1929

HANDBOOK OF MICROSCOPICAL TECHNIQUE FOR WORKERS IN BOTH ANIMAL AND PLANT TISSUES Edited by C E McClung, Ph D, Professor of Zoology, University of Pennsylvania, Director of Zoological Laboratory, University of Pennsylvania Price, \$8 Pp 510, with 43 illustrations New York Paul B Hoeber, 1929

This book is designed for workers in all departments of biologic morphology. It meets the needs of the inexperienced worker who wants specific directions that he can use in handling general material. The major portion of the book describes the latest approved methods for the special technical purposes of experienced investigators. By means of cross references, needless repetition is avoided. The illustrations refer for the most part to instruments and technical procedures in microdissection, micro-injection and the staining of neuroglia and microglia. The book is a reliable and thoroughly competent guide in biologic microtechnology.

EXPERIMENTELLE STUDIEN UBER KNOCHENTRANSPLANTATION UND KNOCHEN-REGENERATION Von Christian Rosing Bull Pp 105, with 17 illustrations Oslo Jacob Dybwad, 1928

COLLOID CHEMISTRY, THEORETICAL AND APPLIED By selected international contributors Collected and edited by Jerome Alexander Volume II Biology and Medicine Price, \$15 50 Pp 992 New York The Chemical Catalog Company, 1928

VERHANDLUNGEN DER DEUTSCHEN PATHOLOGISCHEN GESELLSCHAFT IM AUFTRAG DES VORSTANDES Herausgegeben von dem derzeitigen Schriftfuhrer G Schmorl in Dresden Pp 564, with 148 illustrations Jena Gustav Fischer, 1928

LEHRBUCH DER TOXIKOLOGIE FÜR STUDIUM UND PRAXIS Von Ferdinand Flury, Professor der Pharmakologie an der Universität Würzburg, und Heinrich Zangger, Professor der gerichtl. Medizin an der Universität Zürich Paper Price, 29 marks Pp 500, with 9 illustrations Berlin Julius Springer, 1928

PATHOLOGISCH-ANATOMISCHE VERÄNDERUNGEN ÜBER DIE CONGENITALE SYPHILIS BEI DEM FOETUS UND DEM NEUGEBORENEN KIND Von Oluf Thomsen Paper Price, 20 crowns, Danish Pp 31, with 19 illustrations Copenhagen Levin & Munksgaard, 1928

This is a reprint from a larger work by the author published in Danish in 1912 There are only sixteen pages of text, with nineteen plates in black and white illustrating the microscopic changes in congenital syphilis of the fetus and the new-born infant The book gives a good presentation of the changes in congenital syphilis of the fetus and the new-born infant, but it does not add anything new to the knowledge of those changes

THE KAHN TEST A Practical Guide By R L Kahn, Director of Laboratories, University of Michigan Hospital, Ann Arbor, Michigan Price, \$4 Pp 201 Baltimore Williams & Wilkins Company, 1928

MIKROSKOPISCHER NACHWEIS DER SPIROCHAETA PALIDA, DER GONOKOKKEN UND DES ERREGERS DES ULCUS MOJE Von Dr W A Collier, und Dr A Cohn, Berlin Price, 5 marks Pp 92, with 4 illustrations Berlin Urban & Schwarzenberg, 1928

AMERICAN TYPE CULTURE COLLECTION CATALOGUE OF CULTURES, 1928 Second Edition Pp 142 Chicago American Type Culture Collection, The John McCormick Institute for Infectious Diseases, 1928

VERHANDLUNGEN DES DEUTSCH-RUSSISCHEN SCHARLACH-KONGRESSES VOM 11-14 JUNI, 1928, IN KÖNIGSBERG PR Herausgegeben von Dr T J Burgers, o o Professor für Hygiene an der Universität Königsberg Price, \$5 Pp 400

LECTURES ON CONDITIONED REFLEXES Twenty-Five Years of Objective Study of the Higher Nervous Activity of Animals By Ivan Petrovitch Pavlov, M D, Director of the Physiological Laboratories, Institute of Experimental Medicine and Academy of Sciences, formerly Professor of Physiology, Military Medical Academy, Leningrad, Foreign Member Royal Society, Member of the Russian Academy of Sciences, Nobel Laureate, etc Translated from the Russian by W Horsley Gantt, M D, B Sc, Member of the American Relief Administration 1922 and 1923, co-worker in Professor Pavlov's Laboratory, Institute of Experimental Medicine, from 1925 to 1928 With the collaboration of G Volborth, M D, former assistant to Professor Pavlov at the Military Medical Academy, Professor of Physiology, University of Kharkov An introduction by Walter B Cannon, M D, S D, George Higginson Professor of Physiology, Harvard University Price, \$6 50 Pp 414 New York International Publishers, 1928

## ALEUKEMIC LEUKEMIA AND ATYPICAL LEUKEMOID CONDITIONS

REPORT OF SEVEN CASES INCLUDING ONE OF ACUTE  
ERYTHROBLASTOSIS \*

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Atypical conditions are frequently encountered that clinically and pathologically appear to be borderline cases, showing various mixtures of the characteristics of the acute infections, the purpuras, the anemias and the neoplasms of the blood. The literature relating to these unsatisfactorily classified conditions has become formidable, and one is led rapidly from a consideration of atypical cases of leukemia and pernicious anemia to such seemingly unrelated conditions as Mikulicz' disease (Hannema<sup>1</sup>) and mycosis fungoides (Fraser<sup>2</sup>). Attempts have been made to identify some of these conditions with the leukemias and to separate others from this group and further subdivide them into definite entities. Clinically, they show the greatest diversity. From the pathologic point of view, they shade off into the true leukemias by almost imperceptible degrees. It would seem that a satisfactory classification can be made only when etiologic facts are learned.

The term aleukemic leukemia is commonly applied to an ill-defined group of cases in which the blood picture during life shows severe anemia but does not justify the diagnosis of leukemia, while at autopsy, in addition to leukemia-like cellularity of the bone-marrow, accumulations of myeloid or lymphoid cells are found in the viscera, these accumulations having a qualitative, but usually not a quantitative similarity to

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\* From the Pathological Laboratories of the Peter Bent Brigham Hospital and the Children's Hospital and the Department of Pathology of Harvard University School of Medicine

1 Hannema, L S. Ein Fall von aleukaemischer Myelose mit dem klinischen Bilde von Morbus Mikulicz, *Folia haemat Arch* 32 116, 1926

2 Fraser, J F. Mycosis Fungoides, Its Relation to Leukemia and Lymphosarcoma, *Tr Sect Dermat & Syphilol, A M A*, 1925, p 233

3 Leube, H. Leukanamie, *Deutsche Klin*, vol 3, Diagnostik d inn Krankh Lief 42, p 177, cited by Sternberg in Henke and Lubarsch. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol 1

those found in the true leukemias (The terms leukanemia<sup>3</sup> and pseudoleukemia<sup>4</sup> were formerly applied to such conditions)

The occurrence of foci of myeloid cells in the viscera, in response to extensive destruction of the marrow (as by metastatic carcinoma), has long been recognized, and the question naturally arises whether some of the conditions in which anatomic observations lead to a diagnosis of aleukemic leukemia may not be explained in a similar manner, on the basis of abnormal regenerative activity of the hematopoietic system

The situation is further complicated by the fact that in a great many cases of true leukemia leukopenia spontaneously develops as a terminal event, or at any other time during the course of the disease (King<sup>5</sup>) Furthermore, many cases commonly diagnosed as acute myelogenous leukemia may never show an increased white cell count (King,<sup>5</sup> Galland,<sup>6</sup> Sternberg<sup>7</sup>) The possibility of latent chronic leukemia must be excluded in these cases, and this has often been done

In such cases, the clinical diagnosis must be based on the immaturity of the circulating granulocytes Since Krumbhaar,<sup>8</sup> Herz<sup>9</sup> and others have shown that a high percentage of myelocytes and myeloblasts may be present in the blood stream in cases of severe sepsis, it is obvious that the diagnosis cannot be made from the blood smear alone If recovery takes place, the diagnosis of acute leukemia is usually not adhered to, although cases of this sort have been reported as acute leukemia with recovery (Gutmann<sup>10</sup>) If death occurs and an autopsy is not done, the diagnosis remains doubtful Cases are on record, however, in which, even with a complete autopsy, sepsis of one sort or another has been so obvious that the writer has been tempted to regard the leukemoid infiltration of the viscera as a terminal event, secondary to the infection (Krumbhaar,<sup>8</sup> Sternberg<sup>11</sup>) The visceral infiltration in these cases was, as far as can be learned, always quantitatively less than that typically found in true leukemia, but was sometimes (as in case 7 of the series

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4 Cohnheim Virchows Arch f path Anat **33** 451, 1860

5 King, J J Aleucocythaemic Leukemia, Bull Johns Hopkins Hosp **28** 114, 1917

6 Galland, G L Difficulties in the Diagnosis of Leukemia, Brit M J **2** 108, 1925

7 Sternberg, C Blutkrankheiten, in Henke and Lubarsch Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol 1

8 Krumbhaar, E B Leukemoid Blood Pictures in Various Clinical Conditions, Tr A Am Phys **41** 343, 1926

9 Herz, A Infektionen mit leukamischen Blutbild, Wien klin Wchnschr **39** 835, 1926

10 Gutmann, B Leukemia, Report of an Atypical Case, Am J M Sc **167** 718, 1924

11 Sternberg, C Ueber acute Leukaemie, Wien klin Wchnschr **33** 553, 1920



reported here) equal to that found in cases which, because of their idiopathic nature, have been classified as aleukemic leukemia

The close association of certain types of leukemia with infection has been repeatedly emphasized. The definitely infectious nature of leukosis in the hen (Ellerman<sup>12</sup>) and in the guinea-pig (Snyders<sup>13</sup>), the positive bacteriologic observations in cases of presumably typical acute myeloblast leukemia in man (Sternberg,<sup>7</sup> Catsara<sup>14</sup> and others) and the evidence adduced by such conditions as infectious mononucleosis<sup>15</sup> and its close relative agranulocytosis (Schultz<sup>16</sup>) all strengthen this point of view. Sternberg<sup>7</sup> and others, in fact, sharply separate most acute leukemias from the group of leukemias in general, on the ground that they are acute infectious diseases. (Sternberg recognizes true chronic leukemia with leukopenia and uses the terms leukopenic and lymphopenic leukemia for such cases). Lubarsch similarly suggests a division of the leukemias into primary (cryptogenic) and secondary, these adjectives having the same significance as in their application to the anemias.

The more specific terms, aleukemic myelosis and lymphadenosis (Naegeli), have been used to separate the myeloid forms of aleukemic leukemia from the lymphoid forms. Rare cases of the myeloid type have been described (Jaffé<sup>17</sup>), in which the blood picture constantly shows not only a normal or a low white cell count, but a normal differential count, immature granulocytes being practically absent. Jaffé would restrict the term aleukemic myelosis to these cases, and prefers the term aleukocythemic leukemia for those cases in which immature forms are present in the blood stream in definite and constant numbers. In view of the readiness with which myelocytes and myeloblasts appear in the blood stream in septic conditions, it seems hardly justifiable to separate these cases from otherwise similar cases (case 1 of the series reported below) on this basis alone.

The eight cases to be reported here have been encountered among the routine postmortem examinations at the Peter Bent Brigham Hospital and the Children's Hospital. They have been classified in the following manner: aleukemic leukemia (myelogenous), cases 1 and 2, aleukemic leukemia (myeloblastic), cases 3, 4 and 5, erythroblastosis (acute aleu-

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12 Ellerman, V. *Leucosis of Fowls and Leukemia Problems*, London, Gylndendal, 1921.

13 Snyders, cited by Lubarsch in Henke and Lubarsch. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol 1, p 666.

14 Catsara, J. *Beitrag zur Frage uber die infectiose-toxische Natur der Leukaemischen Erkrankungen*, Virchows Arch f path Anat **249** 43, 1924.

15 Baldrige, C W., Rohner, F J., and Hansmann, G H. *Glandular Fever (Infectious Mononucleosis)*, Arch Int Med **38** 413 (Oct) 1926.

16 Schultz, W. *Ueber eigenartige Halserkrankungen, Monozyten Angina*, Deutsche med Wchnschr **48** 1495, 1922.

17 Jaffe, R H. *Aleukemic Myelosis*, Arch Path **3** 56 (Jan) 1927.

kemic), case 6, leukemoid visceral infiltration secondary to sepsis, case 7, and splenic anemia, eventually (after seven years) appearing as myelogenous leukemia, case 8

A comparative study of these cases was undertaken, and they are reported in order to bring out their general similarity from the anatomic point of view, and their clinical diversity

Acknowledgment should be made of the helpful criticism of Dr S B Wolbach, under whose supervision these cases were studied

#### REPORT OF CASES

**CASE 1—History**—A man, aged 52, entered the hospital complaining of pain and soreness in the joints of the arms and the legs. This pain began four and a half months before entry, and was almost constantly present following that, but with numerous acute exacerbations. During these severe attacks, he felt feverish and on several occasions had definite chills. He lost 20 pounds (9 Kg) in weight after the onset of his illness. He had previously been strong and well with the exception of an isolated attack of pain and swelling in the joints of his right arm at the age of 22, which lasted for four weeks.

**Examination and Course of the Disease**—The results of the physical examination were essentially negative. During the ten weeks that followed (up to the time of the patient's death) there was a sharp daily rise in temperature (often to 105 F). Typhoid fever, endocarditis and malaria were considered as diagnostic possibilities, but the Widal reaction was negative, malarial parasites were not found in the blood stream and repeated blood cultures (aerobic and anaerobic) were negative. Repeated examination of the blood during the ten weeks of observation showed an increasing anemia (the count of red cells falling steadily from 3,120,000 to 1,116,000) and a constant leukopenia (the count of white cells ranging from 3,900 to 6,500). The differential count was essentially normal except for the presence of from 4 to 6 per cent myelocytes and of from 1 to 2 per cent nucleated red cells.

**Postmortem Examination**—Postmortem examination was made thirteen hours after death. Petechial hemorrhages were noted on the chest, the thorax and the arms. The bronchial and the mesenteric lymph nodes were slightly enlarged, the largest being 1 cm in its greatest dimension. The spleen weighed 690 Gm, and was flabby. On section, the normal markings were obscured, and the pulp was soft and reddish purple in color. The esophagus showed several areas of ulceration in its lower half, otherwise the gastro-intestinal tract was normal. Peyer's patches and the solitary lymph follicles were not unusually prominent. The liver weighed 2,190 Gm and was considered to be somewhat enlarged. It was normal in consistency, and the markings were fairly prominent, but leukemic infiltration could not be made out in gross. The bone marrow in the femur, the ribs, and the right clavicle was markedly hyperplastic and ivory white. In different regions, it varied in consistency from soft to moderately firm (the consistency of normal spleen).

**Microscopic Examination**—**Bone Marrow** There was marked hyperplasia, and almost complete replacement of the normal constituents by atypical cells, so that the tissue was almost unrecognizable. An outstanding feature was the presence of large numbers of giant cells, some of which contained each a great many apparently separate nuclei, and others of which appeared to contain each a single multilobulated gigantic nucleus. These large single nuclei were either swollen and edematous in appearance, or hyperchromatic and irregular in outline. The nuclei of these cells were composed of a delicate chromatin network. Their

cytoplasm was irregular in shape and usually homogeneous, and it varied in its staining reaction from eosinophil to basophil (fig 1). Occasionally, these cells contained phagocytosed erythroblasts, or cells resembling polymorphonuclears.

In addition to the giant cells, many single cells were present. These cells were polygonal or elongated in shape and had each a large round or oval nucleus, composed of finely divided chromatin (resembling the nucleus of a megaloblast) and a moderate amount of stippled or reticulated (basophil or eosinophil) cytoplasm. These cells, except for the difference in size, were similar to many of the giant cells, and the impression was strong that they were fundamentally the same type of cell, probably hypertrophic reticular cells or endothelial cells. The giant cells occasionally showed the cytoplasmic differentiation characteristic of the megakaryocyte. A few myelocytes and nucleated red cells were present, but adult granulocytes and

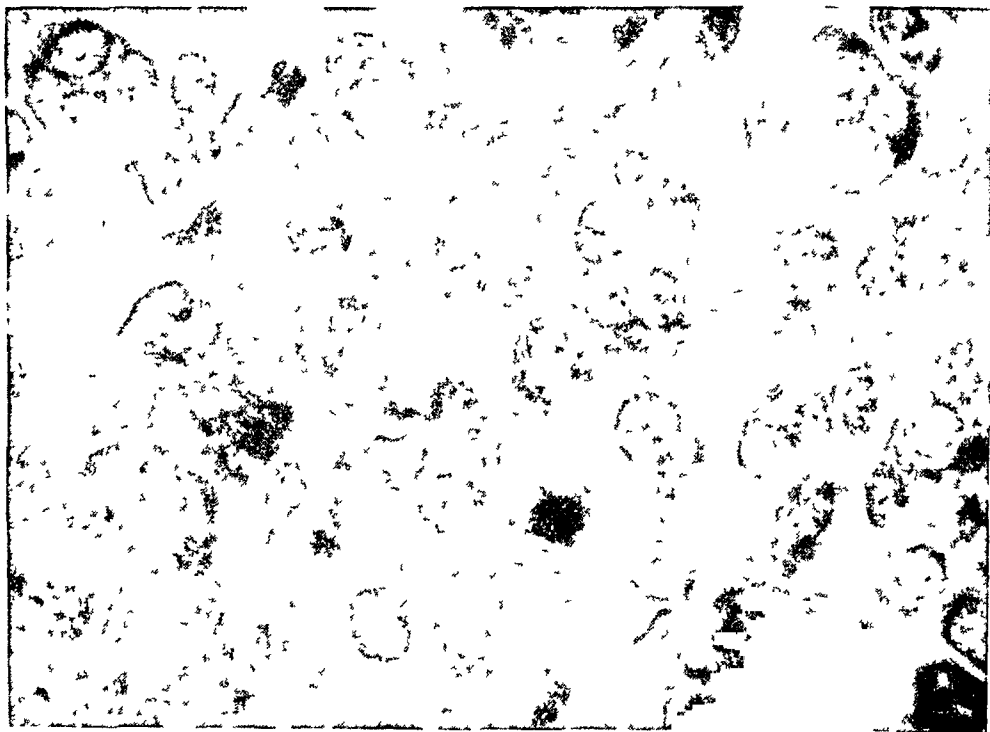


Fig 1 (case 1) —A high magnification of the bone marrow in a case of aleukemic myelogenous leukemia (giant cell type). Large atypical single and multinucleated cells of a primitive type may be seen. One characteristic mitotic figure is shown. Phosphotungstic acid-hematoxylin stain,  $\times 1,200$ .

erythrocytes (except within blood vessels) were practically absent. Blood vessels recognizable as such were few in number, and there were many areas of definite fibrosis (fig 2). Mitotic figures were numerous, and the resemblance to tumor tissue was, in many areas, striking, and the tissue would have been so regarded except for its weak powers of invasion.

**Heart** Several of the smaller vessels were apparently plugged with cells resembling early myelocytes.

**Lungs** There was marked edema, and a few petechial hemorrhages were seen. Beneath the pleura and in the peribronchial tissue, there were several small areas of fairly dense connective tissue formation. In these areas there were numerous gigantic cells, with irregular, swollen or hyperchromatic, multilobulated nuclei. These cells were frequently undergoing multiple mitosis.

In addition to these large cells there were many smaller cells with basophil cytoplasm, having the appearance of myeloblasts or early megaloblasts, a few definite myelocytes and an occasional island of nucleated red cells. The frequency of mitotic figures gave evidence of the proliferation of these cells in situ. They appeared to be developing from undifferentiated local mesenchymal elements, but it is of course possible that their progenitors may have been metastatic from the marrow. The appearance of these pleural and peribronchial foci was strikingly similar to that of the bone marrow in this case.

**Spleen** The pulp was cellular, and the trabeculae were widely separated. The malpighian corpuscles were not seen. The reticular spaces were distended with myeloid cells, including undifferentiated elements, myelocytes, nucleated red cells and many atypical gigantic cells, so that this tissue, also, had much the same appearance as the bone marrow. Mitotic figures were numerous, especially in the elongated cells lining the reticular spaces. There were moderate hemosiderosis and moderate diffuse fibrosis.

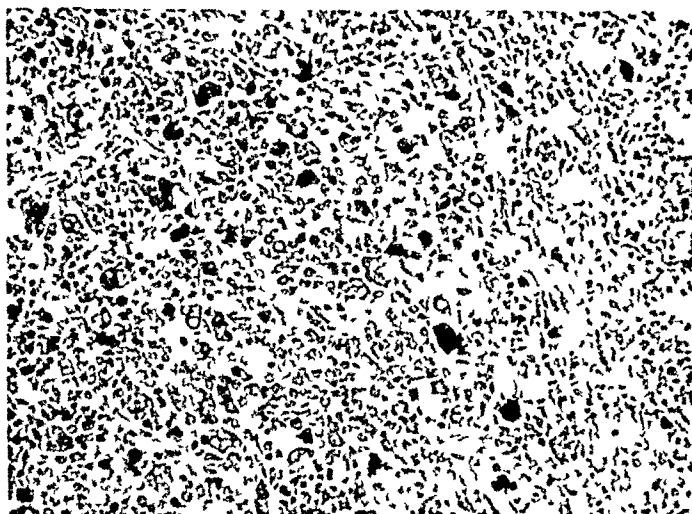


Fig 2 (case 1) —A low magnification of marrow from the femur in a case of aleukemic myelogenous leukemia (giant cell type). Giant cells and fibrosis may be seen, eosin-methylvale blue stain,  $\times 160$

**Liver** The sinusoids contained scattered cells (occasionally in small clusters). Many nucleated red cells were present, as well as myelocytes, myeloblasts and atypical giant cells. Except for the atypical nature of many of the cells, the picture bore a striking resemblance to that of hematopoietic activity in the liver of a newly born infant. The portal areas contained only a few lymphocytes.

**Lymph Nodes** Sections of mesenteric, retroperitoneal and bronchial nodes all showed myeloid activity similar to that observed in the spleen. Nucleated red cells were numerous. There was considerable fibrosis in some sections. The surrounding fatty tissue had undergone myeloid transformation in focal areas, and here atypical giant cells were especially numerous (fig 3).

**Esophagus** The usual changes characteristic of an acute ulcer were found.

**Bacterial Stains** Organisms could not be demonstrated in sections of the various organs stained by the Giemsa method. Ziehl-Neelsen stains did not reveal acid-fast rods or granules.

*Diagnosis*—Hyperplasia and anaplasia<sup>18</sup> of the bone marrow, myeloid metaplasia of the spleen, liver and lymph nodes, fibrosis of the bone marrow, spleen and lymph nodes, anemia, splenomegaly, hepatomegaly (slight), esophageal ulceration, petechial hemorrhages of the lungs, pleura, and pericardium, edema of the lungs, and aleukemic myeloid leukemia (giant cell type)

*CASE 2—History*—A man, aged 61, who had always been in good health except for typhoid fever at the age of 37, entered the hospital complaining of weakness and pallor. Thirteen months before admission he had had whooping cough. From this time, he felt that he had never recovered his full strength. Five months before entry he first noticed definite weakness and pallor, and at about the same time petechial hemorrhages appeared on his legs. It was thought that he had pernicious anemia, and three transfusions were done, which were followed with slight temporary improvement.

*Examination and course of the disease*—There was marked pallor, without, however, loss of weight. Recent and old retinal hemorrhages were noted. The edge of the liver was palpable, but the spleen could not be felt.

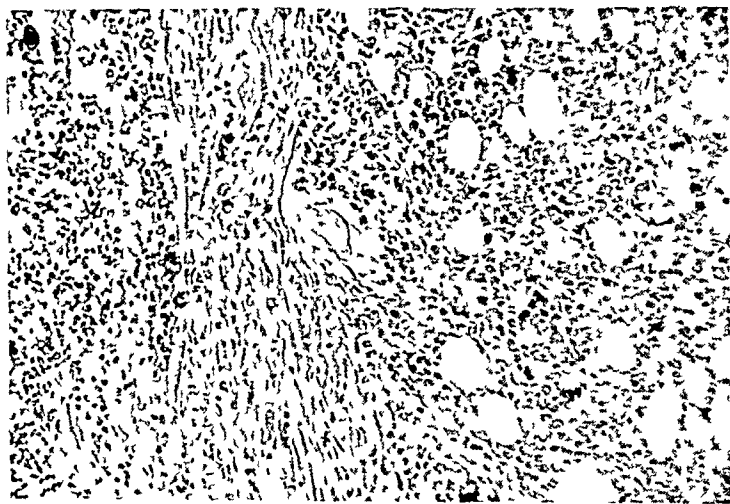


Fig 3 (case 1)—A peripheral sinus and capsule of a lymph node (in the left third of the figure) and adjacent mesenteric fat (at the right). Note the atypical myeloid reaction in the mesenteric fatty tissue, and the resemblance of this tissue to hyperplastic bone marrow. Several giant cells are present, eosin-metheylen blue stain,  $\times 160$ .

The patient was under observation (except for an interval of about seven weeks that he spent at home) for the four months preceding his death. During this time, he occasionally showed a slight rise in temperature, which was never higher than 100 F, except for a terminal rise to 102. Purpuric spots appeared on the legs on two occasions. In spite of a diet rich in liver, the anemia became more severe, and he died rather suddenly, complaining of pain in the right side of the chest.

Examination of the blood made at intervals during the four months' observation showed a constant leukopenia (the count of white cells ranging from 2,100 to 2,500) and a normal differential count, except for the appearance of 2 per cent

18 This term is used to signify the extensive replacement of the normal constituents of hyperplastic marrow by primitive, undifferentiated elements.

myelocytes in the last count, 48 hours before the patient's death. During this period, the count of the red cells fell from 3,000,000 to 1,500,000, and from 10 to 12 per cent normoblasts were frequently noted in the differential count. The bleeding and clotting times were normal. The color index was always above 1, and the smear showed a picture similar to that of pernicious anemia. Free hydrochloric acid was present in the contents of the stomach in small amounts.

The differential diagnosis lay between pernicious anemia and aleukemic leukemia, and the latter diagnosis was made by the hematologist. It is of interest to note that the failure of the anemia to improve under the therapeutic administration of liver was considered a possibly important point in ruling out pernicious anemia.

*Postmortem Examination*.—Postmortem examination was made six hours after death. The body was well developed and well nourished. The skin was smooth and pale. The subcutaneous fat was lemon yellow. The mesenteric, retroperitoneal, bronchial, cervical and inguinal lymph nodes were not enlarged. The heart weighed 440 Gm. Petechial hemorrhages were noted on the epicardium.

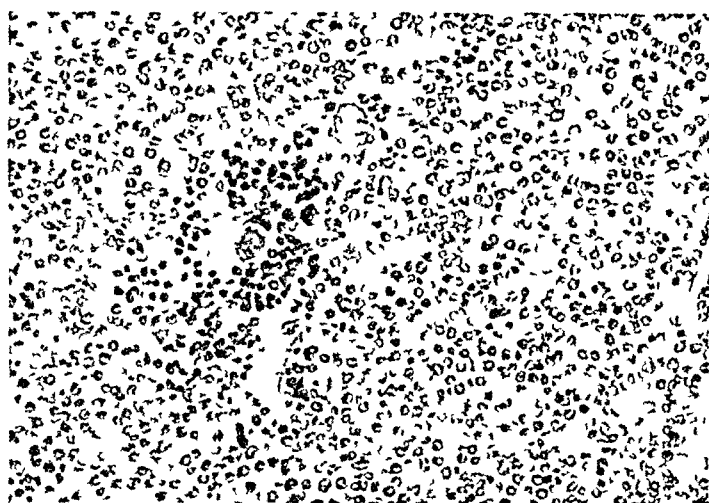


Fig 4 (case 2).—A low magnification of marrow from the femur in a case of aleukemic myelogenous leukemia. Uniform primitive cell hyperplasia and one island of erythroblasts may be seen. eosin-methylene blue stain,  $\times 160$ .

The pleural cavities each contained about 300 cc of clear fluid. The lungs were markedly edematous. The spleen was moderately enlarged (240 Gm). Its gross appearance was not remarkable. The liver which was enlarged, weighed 2,380 Gm. It was light brown and uniformly mottled with small opaque areas slightly larger than milary tubercles, which were recognized grossly as areas of leukemic infiltration. The kidneys weighed 200 and 190 Gm, and were not considered abnormal in gross. The bone marrow in the femur and the ribs was markedly hyperplastic, and it filled the marrow space to the exclusion of fatty tissue and bone trabeculae. It was deep reddish purple.

The other organs did not show changes of importance.

*Microscopic Examination*.—*Bone Marrow*. The marrow was markedly hyperplastic, the great majority (about 95 per cent) of the cells being undifferentiated elements with rounded vesicular nuclei and scanty, pale, nongranular cytoplasm. The majority of these cells corresponded in appearance to early myeloblasts. There were scattered clusters of somewhat larger cells, with more abundant, bright blue, irregularly stippled cytoplasm. Islands of nucleated red cells were con-

spicuous in some regions, and myelocytes were fairly numerous. Adult red cells were numerous, but adult granulocytes were practically absent. Mitotic figures were fairly numerous. Giant cells of the type previously described in case 1 were present in somewhat larger numbers than the megakaryocytes of active normal marrow. There was slight fibrosis in a few areas.

**Spleen** The malphigian corpuscles were reduced in number and small. In some areas there were marked congestion and diffuse hemorrhage. The pulp was cellular, and the reticular spaces were filled with cells of the myeloid series, myeloblasts predominating, with here and there small groups of eosinophil myelocytes. Islands of erythroblasts were also present in some areas. Giant cells were fairly prominent, some of which appeared to be typical megakaryocytes, while others appeared to be atypical cells similar to those seen in case 1. Occasional mitotic figures were present. There was definite fibrosis in circumscribed areas. These

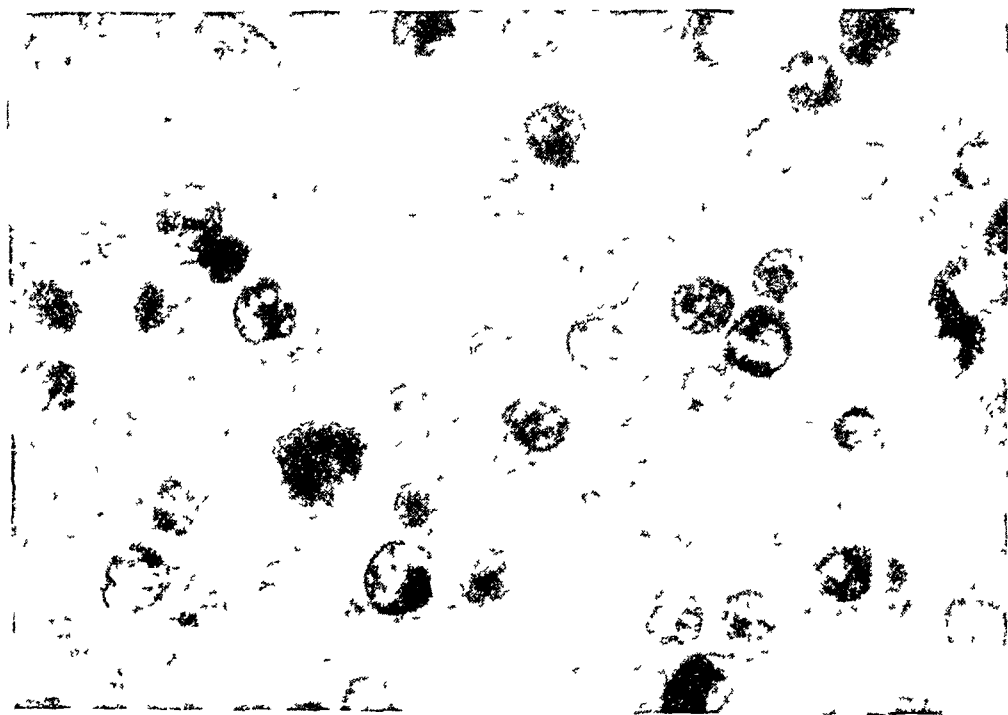


Fig 5 (case 2) —A high magnification of a portion of the field shown in fig 4, eosin-methylene blue stain,  $\times 1,200$

areas of fibrosis often contained small central vessels, giving the impression that they took origin in malphigian corpuscles. There was marked hemosiderosis.

**Lymph Nodes** Sections of bronchial lymph nodes showed myeloid activity similar to that observed in the spleen. The capsules of the nodes showed an increase of connective tissue. The myeloid change in several areas had also extended to the surrounding fatty tissue.

**Liver** The milary nodules described grossly were largely portal in situation. They were so large and numerous that they composed approximately one third of the total substance of the liver. There was evidence of pressure atrophy of the adjacent liver cells. The intervening liver sinusoids contained scattered cells and occasionally small clusters of cells. The Kupffer cells were everywhere prominent. The cells composing these aggregations for the most part resembled myeloblasts or early myelocytes, with a fairly plentiful sprinkling of eosinophil myelocytes and a few nucleated red cells.

**Kidneys** Aggregations of cells entirely similar to those seen in the liver were found scattered through the kidney substance, sometimes intertubular, but more often perivascular in location. In the pelvic fatty tissue, also, small islands of these cells were seen, among which were occasional large elongated cells, the appearance of which suggested an origin from primitive mesenchymal cells.

**Bacterial Stains** Bacteria were not found in sections of the various organs stained by the Giemsa method, nor could acid-fast rods or granules be demonstrated.

**Diagnosis**—Hyperplasia and anaplasia of the bone marrow, myeloid metaplasia of the spleen and the lymph nodes, leukemic cellular aggregations (myeloid metaplasia?) in the liver and the kidneys, anemia, splenomegaly (slight), hepatomegaly, and aleukemic myelogenous leukemia.

**CASE 3—History**—A woman, aged 58, with an unimportant past history, entered the hospital complaining of fever and weakness of one month's duration. The onset was fairly sudden and associated with small tender glands in the back

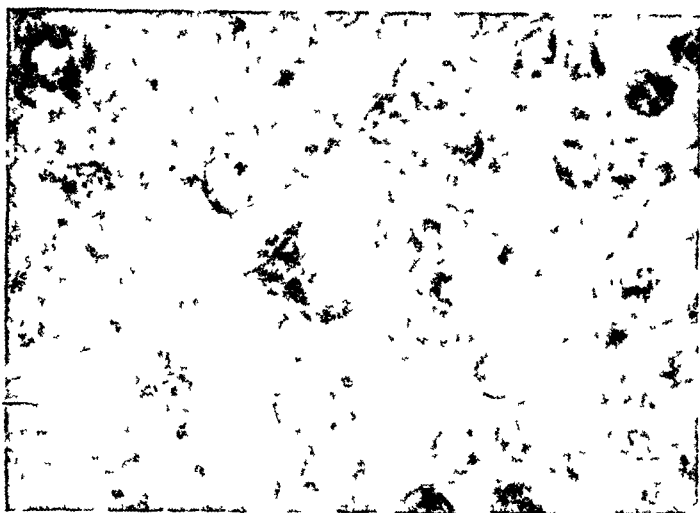


Fig 6 (case 2) —The edge of a colony of undifferentiated cells in the liver in a case of aleukemic myelogenous leukemia, eosin-methylene blue stain,  $\times 1,000$

of the neck near the scalp line. Herpes labialis developed one week later. One week before entry she was forced to go to bed.

**Examination and Course of the Disease**—The results of the physical examination were essentially negative except for slight pallor, and a questionably palpable spleen. Bacteriologic and serologic tests for the typhoid group were negative. Free hydrochloric acid was absent in the fasting stomach contents, but normal after the test meal. The tongue was smooth but not characteristic of pernicious anemia. The white cell count varied from 1,500 to 2,100, but was more frequently near the lower figure. The differential count showed from 80 to 91 per cent lymphocytes and from 8 to 20 per cent polymorphonuclears. Large mononuclears, eosinophils, mast cells and myelocytes were absent. A rare normoblast was seen. The red cell count dropped steadily from 3,120,000 to 1,160,000. The color index was always considerably greater than unity. Anisocytosis and poikilocytosis were striking. A blood culture on entry was negative, but on the day before death a positive culture of *Bacillus pyocyaneus* was obtained. Death occurred one month after entry.



The clinical diagnosis was obscure, but the blood picture was that of pernicious anemia and this diagnosis was made in spite of the atypical acute course, the presence of hydrochloric acid in the stomach contents and the definite suggestion of obscure sepsis. There was a daily rise in temperature (to from 102 to 103 F) during the entire period of observation, with a terminal rise to 105 F.

*Postmortem Examination*—Postmortem examination was made six hours after death. The body was well developed and nourished. The skin showed a yellowish pallor. The spleen weighed 520 Gm. It was soft and deep purple. The liver was normal in size and light yellow. The kidneys were small and irregularly mottled. Bone marrow removed from the femur was markedly hyperplastic and deep red.

*Microscopic Examination*—*Bone Marrow* The marrow was cellular in appearance (fig 7 A), and was composed almost entirely of rather small cells with pale, often indented nuclei. These cells were believed to be hematocytoblasts, or primitive blood cells. Differentiated elements were practically absent from the marrow, and only an occasional myelocyte was seen. Rarely, a small island of nucleated red cells was encountered. The striking feature of the undifferentiated cells present in this marrow was their irregularity (fig 7 B). The nuclei were frequently clover shaped or dumb bell shaped, the cytoplasm conforming to the shape of the nucleus, this appearance suggested that they were in active ameboid movement.

*Spleen* There was marked congestion, and the only abnormality that could be made out was the presence in the pulp of large numbers of undifferentiated cells similar to those described in the bone marrow.

*Liver* The portal areas were heavily crowded with similar undifferentiated cells (fig 7 C), and these cells were also scattered through the sinusoids. Quantitatively, the accumulations of abnormal cells were comparable to those seen in true leukemia, although it is to be noted that the liver was not enlarged in gross.

*Kidneys* Here again, undifferentiated cells had accumulated between the tubules and around the glomeruli and the blood vessels to such an extent that the appearance was that of a true leukemic infiltration. In the centers of these areas of cellular aggregation, sclerosed glomeruli were frequently seen, but it was not possible to determine whether this condition was secondary to the cellular accumulation or was previously existing and unrelated. These abnormal cells had nuclei that were rather irregular in shape (often elongated or dumb-bell shaped) and composed of a spongelike chromatin network, in which were usually one or more nucleoli. Their cytoplasm was scanty, and it was usually drawn out into long thin processes. Their appearance was similar to that of the hemohistioblasts of Ferrata, as described by Richter<sup>19</sup>. Connective tissue cells of various ages were intermingled with them, and it seemed possible to trace the evolution of the abnormal cells through various intermediate stages back to these mesenchymal elements. A few eosinophil and basophil myelocytes and an occasional small group of nucleated red cells were intermingled with the more primitive cells.

*Lymph Nodes* The lymph nodes also showed a marked increase in undifferentiated cells similar to those in the other organs.

*Bacterial Stains* Sections of the various organs stained by Giemsa's method were carefully studied. A few clumps of bacilli were found within blood vessels in the liver, but otherwise the results were negative. Stains for acid-fast organisms were negative.

19 Richter, M. N. Hemohistioblast of Ferrata, *Am P M Sc* **169** 336, 1925

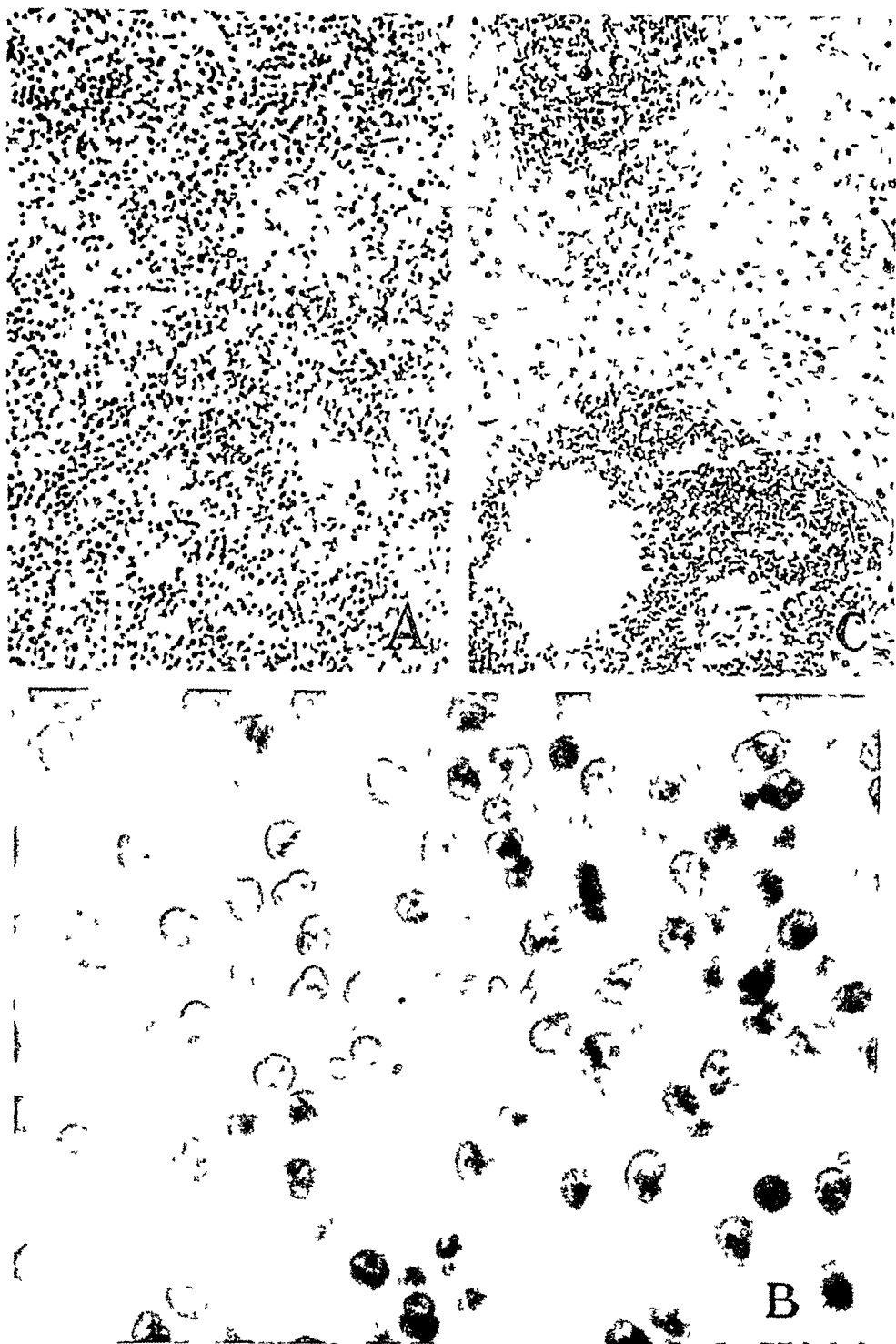


Fig 7 (case 3) —Aleukemic (myeloblastic?) leukemia *A* presents a representative view of marrow from the femur showing uniform undifferentiated cell hyperplasia. The cells are small and hyperchromatic, eosin-methylene blue stain,  $\times 160$ . *C*, portal aggregations of cells in the liver with small collections in the sinusoids, eosin-methylene blue stain,  $\times 100$ . *B*, a high magnification of the bone marrow showing one large reticulum cell at the left, and many small cells with deeply stained irregularly lobulated nuclei. Adult granulocytes were completely absent and myelocytes extremely difficult to find in this marrow, eosin-methylene blue stain,  $\times 1,200$ .

*Diagnosis*—Hyperplasia and marked anaplasia of the bone marrow, myeloid metaplasia of the spleen, liver, kidneys and lymph nodes, anemia, splenomegaly, and acute aleukemic leukemia ("stem cell" type?)

*CASE 4—History*—A girl, aged 16, entered the hospital complaining of nosebleeds. She had always been well, except for the usual diseases of childhood and an attack of influenza in 1918 (eight years before entry to the hospital). Eight weeks before admission, she began to be attacked with nausea and vomiting (of food just eaten). She became weak, and four weeks before entry began to have profuse nosebleeds, which recurred frequently thereafter. At this time, she had a temperature of 102 F, and a mass in the upper right side of the abdomen. A laparotomy revealed only a large liver.

*Examination and Course of the Disease*—The patient was poorly nourished and pale. The liver was definitely enlarged to palpation, but the spleen could not be felt. A few firm, pea-sized lymph nodes were felt in the left axilla and in the groins.

Examination of the blood showed a severe anemia (a red cell count of 1,640,000 dropping to 1,120,000 before death) and leukopenia (the white cell count being from 3,450 to 1,200). The differential count showed from 35 to 50 per cent polymorphonuclears and from 48 to 64 per cent small mononuclear cells, which were considered to be abnormal lymphocytes. A few nucleated red cells were seen, but not any myelocytes. The bleeding time was six minutes and the clotting time one minute. The fragility of the red cells was slightly increased. During the two months of observation there was an irregular fever (to 102 or 103 F on several occasions). She continued to have nosebleeds and two transfusions gave only slight temporary relief. For one week previous to her death, she complained of severe pain in the region of the enlarged liver.

*Postmortem Examination*—This was done eight hours after death. The body was markedly emaciated. Petechial hemorrhages were present over the chest and the abdomen. The mesenteric lymph nodes were moderately enlarged and numerous. The heart was normal, except for petechial hemorrhages on the pericardium. The left lung contained a single small patch of early bronchopneumonia. The liver weighed 2,160 Gm. It was fatty in appearance, and minute nodules of leukemic infiltration could be made out with difficulty. The spleen weighed 150 Gm. It was red and pulpy, but otherwise not remarkable. The kidneys weighed 240 and 220 Gm. They showed subcapsular hemorrhages and a striking nodular leukemic infiltration. The bone marrow from the femur was moderately hyperplastic and red, and had caused some atrophy of the bony trabeculae, but in sharply localized areas it was still fatty in appearance. The other organs did not show important changes.

*Microscopic Examination*—Heart. In the pericardial fat there were definite cellular aggregations. These groups of cells were composed largely of medium-sized cells with pale rounded nuclei, but occasional eosinophil and basophil myelocytes and rare nucleated red cells were also present, as well as elongated cells suggesting a mesenchymal origin. The appearance of this fatty tissue was similar to that of early regeneration in fatty bone marrow. Small cellular aggregations of a similar nature were seen in the heart muscle, usually in a perivascular position.

*Spleen*. There was extreme congestion. The malpighian corpuscles were irregular in size and shape but, on the whole, not increased in prominence. Many of them showed central fibrosis and were nearly obliterated. There was moderate hemosiderosis. The pulp was markedly increased in cellularity, the predominating

cell being consistent in appearance with the lymphoblast or the myeloblast. Myelocytes and nucleated red cells were fairly numerous, however, and mitotic figures were frequently seen.

**Liver** The picture was that of central hemorrhage and necrosis, with heavy leukemic infiltration, which was for the most part periportal.

**Kidney** The tumor-like nodules described grossly were seen to be areas of dense leukemic infiltration. The cells lay between the tubules (fig 8 C), and mitotic figures were numerous. The cells nearly all had rather large, often indented pale nuclei with a delicate chromatin network and a narrow rim of pale blue staining cytoplasm. It was impossible, on morphologic grounds, to say whether they were myeloblasts, erythrogonia or atypical lymphocytes, but because of the presence of a few typical granular myelocytes they were believed to be early cells of the myelocytic series.

**Lymph Nodes** The lymph nodes were cellular in appearance. There seemed to be a uniform filling of the lymph channels with the same cells seen in the other organs. The lymph follicles were everywhere obliterated. Mitoses were numerous.

**Bone Marrow** This was hemorrhagic and moderately hyperplastic. Here, as in the other organs, most of the cells were consistent in appearance with myeloblasts, early megaloblasts or abnormal lymphocytes (figs 8, B and C). However, islands of fatty tissue alternated with the cellular areas. Islands of nucleated red cells were fairly frequent, while granulocytes were few.

Sections of the other organs did not show changes of importance.

**Bacterial Stains** The blood vessels in the heart and the spleen often contained large masses of cocci, and the epithelial cells lining the kidney tubules were often heavily loaded with bacilli. Acid-fast organisms could not be demonstrated.

**Diagnosis**—Moderate hyperplasia and marked anaplasia of the bone marrow, leukemic colonization in the liver, spleen, kidneys and lymph nodes, petechial hemorrhages in the pericardium, liver, kidneys and skin, fatty degeneration of the liver, anemia, bronchopneumonia, and aleukemic (myeloblast) leukemia.

**CASE 5—History**—A boy, 3 years of age, previously well, was brought to the hospital because of an increasing pallor of seven months' duration.

**Examination and Course of the Disease**—The child was well nourished but apathetic. The results of the physical examination were otherwise essentially negative. The red cell count was 1,096,000, and the hemoglobin 25 per cent. The red cells were almost without abnormalities. The white cell count was 5,500, with 21 per cent polymorphonuclears and 79 per cent lymphocytes, many of which appeared to be abnormal. The blood smear was examined by a hematologist of wide experience, who made a note that it showed an undertermined type of anemia and that, aside from the anemia, there was not any positive evidence of a serious blood disorder. In spite of a transfusion and a diet rich in liver and iron, the anemia became more severe and four weeks after entering the hospital the child developed air hunger and died. The blood picture, except for the increasing anemia, did not change in any significant manner during the period of observation. There was a slight irregular fever during the period of observation (from 97 to 100.6).

**Postmortem Examination**—Postmortem examination was made three hours after death. The development and nourishment were found good. The skin was pale and had a slightly yellowish tinge. Grossly, aside from the anemia, the only important abnormality was observed in the bone marrow. Marrow from the femur was found to be hyperplastic, with atrophy of the bone trabeculae. It was dark pink and soft but not gelatinous. Marrow from the ribs was a normal deep

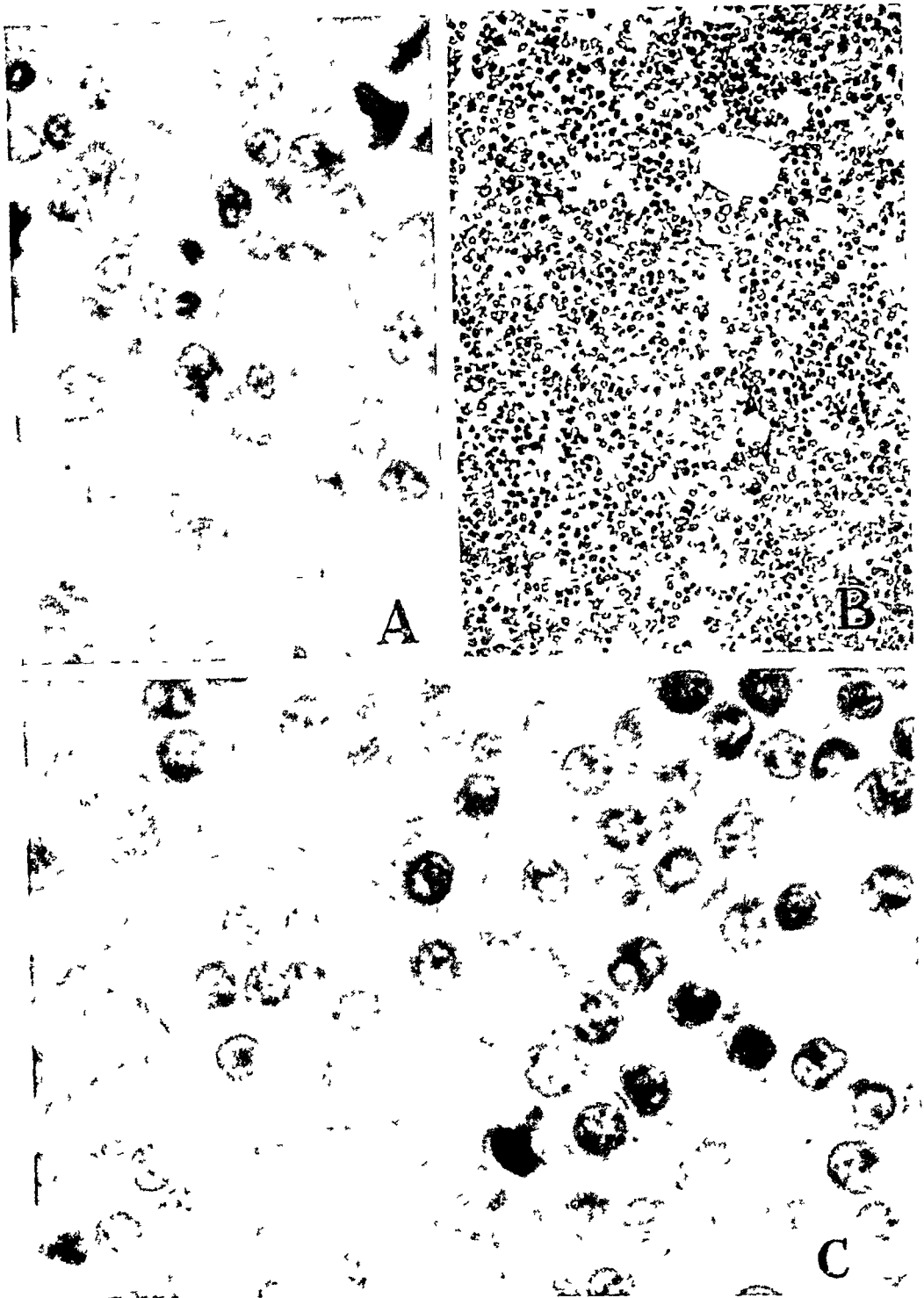


Fig 8 (case 4)—Aleukemic (myeloblast) leukemia. *A*, a collection of cells between a glomerulus and a tubule in the kidney, eosin-methylene blue stain,  $\times 1,000$  *B*, marrow from the femur in a localized area of hyperplasia. The deeply stained cells are mostly nucleated red cells, eosin-methylene blue stain,  $\times 160$  *C*, a high magnification of the marrow showing undifferentiated cells resembling large lymphocytes, eosin-methylene blue stain,  $\times 1,200$

red and not noticeably hyperplastic. The mesenteric lymph nodes were slightly enlarged (the largest being 6 mm in diameter). Bronchial, mediastinal and cervical nodes were not enlarged. The spleen, kidneys, liver, pancreas, lungs, suprarenal gland, bladder and gastro-intestinal tract appeared grossly normal. The prussian blue reaction was strongly positive on the liver and the spleen, but negative on the tissue of the lung and the kidney.

*Microscopic Examination*—**Bone Marrow** The bone marrow was markedly hyperplastic, being composed chiefly of nucleated red cells and small cells of an unclassifiable nature resembling lymphocytes (fig 9 A). The cells lacked, however, the typical nuclear structure of the ordinary small lymphocyte, and their nuclei showed much more irregularity of shape (fig 9 B). They were believed to be of the myeloid series (the so-called micromyeloblasts) rather than lymphoid cells, although the evidence for this view was not complete. Myelocytes were present in moderate numbers. Adult red cells were fairly numerous.

**Heart** The heart muscle fibers contained much fat.

**Spleen** There was marked hematopoietic activity. The splenic corpuscles were numerous but not prominent, owing to the enormous increase of cells in the pulp. These cells were of four types: elongated cells with abundant cytoplasm (hemohistiocytes?), smaller cells consistent in appearance with myeloblasts or polymorphocytes, small dark cells resembling those described in the marrow and erythroblasts. The relative proportion of the last two types was difficult to determine, but otherwise these four types of cells appeared about equally numerous. Hemosiderin was inconspicuous.

**Liver** Marked fatty infiltration was observed about the central veins, but not any leukemic infiltration.

**Kidneys** There were definite periglomerular, perivascular and intertubular collections of small unclassifiable cells resembling those found in the marrow (fig 9 C). Among these cells were definite small clumps of staphylococci, often intracellular. Nucleated red cells were not seen here. The tubular epithelium was uniformly and heavily laden with fat.

**Lymph Nodes** These were hyperplastic and their capsules were over-run. The changes were similar to those in the spleen.

**Bacterial Stains** Except in the lesions of the kidney (as noted above) bacteria were not found in Giemsa-stained sections of the various organs. Acid-fast stains were negative.

*Diagnosis*—Hyperplasia and anaplasia of the bone marrow, myeloid metaplasia of the kidneys, spleen and lymph nodes, fatty infiltration of the heart, liver and kidney, edema of the lungs, and aleukemic (myeloblastic) leukemia (?).

**CASE 6—History**—A boy, aged 7½ years, the fourth child of healthy parents, had been well until seven weeks before entry into the hospital, at that time he began to have diarrhea, which became more and more severe. Aside from weakness there had not been other symptoms.

*Examination and Course of the Disease*—The results of the physical examination, except for emaciation, pallor, a distended abdomen and slight generalized glandular hyperplasia, were essentially negative. Proctoscopic examination did not reveal any ulcerations of the lower part of the colon. The diarrhea was so severe that ileostomy was considered necessary to save the patient's life, but he died before this could be done (two weeks after admission).

The blood picture on entry showed 31,000 white cells, of which 90 per cent were considered to be atypical small lymphocytes, 9 per cent polymorphonuclears and 1 per cent myelocytes. The white cell count during the next week fell to

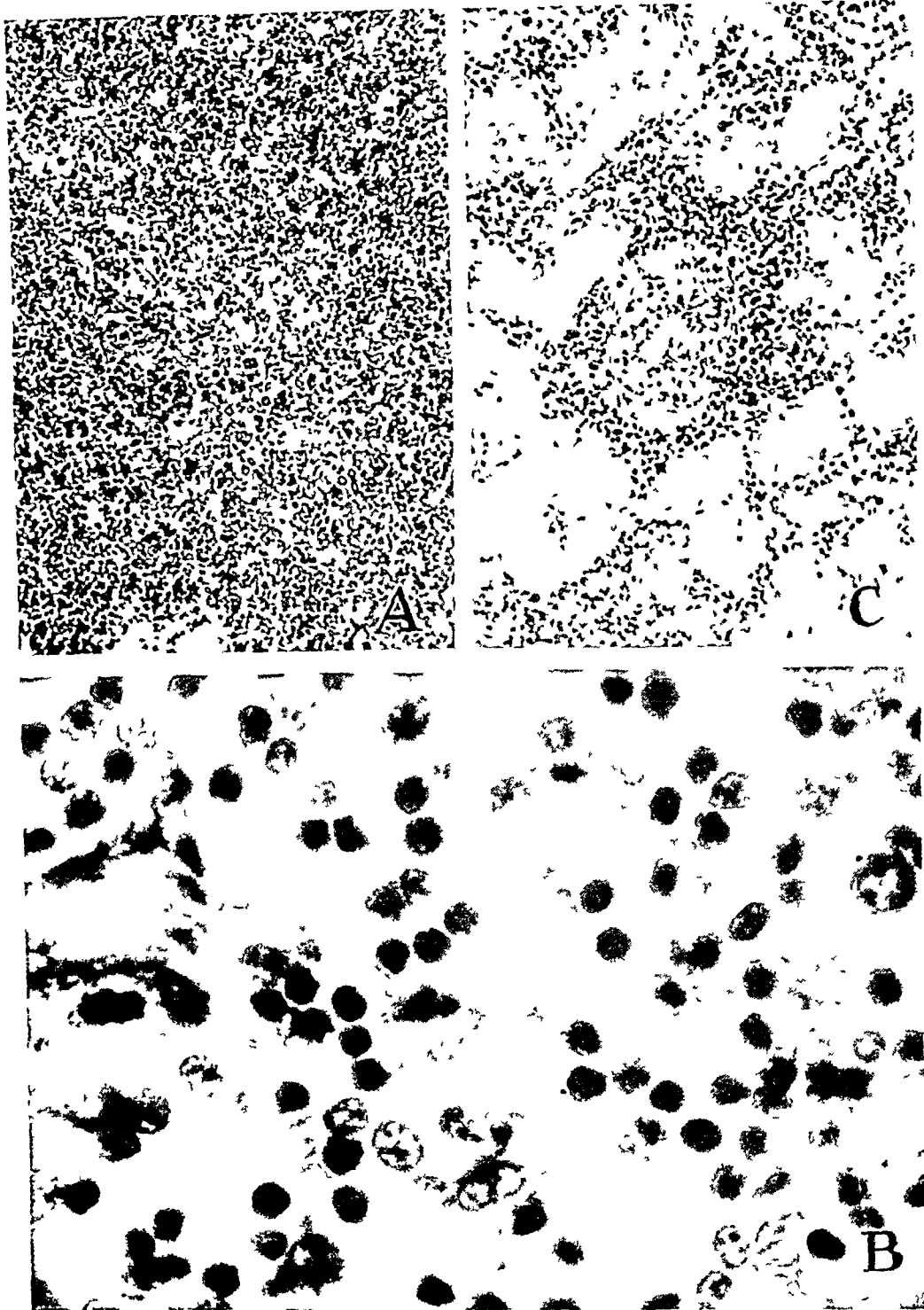


Fig 9 (case 5)—Aleukemic (myeloblast?) leukemia *A*, marrow from the femur showing extreme cellularity. The small size of the cells should be noted (compare with fig 4), which was taken at the same magnification, eosin-methylene blue stain  $\times 160$  *B* a high magnification of the marrow showing scattered reticulum cells and many small cells with hyperchromatic nuclei, some of which are nucleated red cells, while others are primitive cells of lymphoid appearance (see fig 12), eosin-methylene blue stain,  $\times 1,200$  *C*, periglomerular and intertubular aggregations of cells in the kidney, comparable to those seen in true leukemia, eosin-methylene blue stain,  $\times 160$

11,000, the differential count remaining essentially unchanged, except that 10 per cent myelocytes were found. Further leukocytosis was not observed. The red cell count during this period varied between 3,850,000 and 2,450,000 (hemoglobin being from 45 to 65 per cent). Nucleated red cells were "numerous." Stool examinations and Widal reactions revealed nothing abnormal. The temperature rose to 100 F. on three occasions during the period of observation.

*Postmortem Examination*—Postmortem examination was made four hours after death. The body was found poorly nourished. There was a small amount of bloody fluid (75 cc.) in the peritoneal cavity, and the peritoneum was everywhere dull and sticky. Impression smears showed "lymphocytes" and a rare polymorphonuclear, but not any bacteria. The mesenteric lymph nodes were moderately enlarged. The lungs showed early acute bronchopneumonia. The spleen was somewhat enlarged (100 Gm.) and was deep red but otherwise not remarkable. The mucosa of the ileum and of the colon was slightly injected in a few areas, and a small amount of mucinous material was adherent to the surface of the colon. There was not, however, any gross evidence of an important enteritis. The bone marrow was obtained from the second lumbar vertebra only, in which it was dark red but had not caused atrophy of the trabeculae. The other organs appeared normal.

*Microscopic Examination*—The pericardium and pericardial fatty tissue contained focal collections of extremely small cells with dark, homogeneous nuclei. Many of these had definite erythrocytoid cytoplasm and were typical erythroblasts.

*Spleen* The architecture, on the whole, was not markedly disturbed. The striking feature was the tremendous number of nucleated red cells that this tissue contained. These cells were numerous in the sinusoids, but were especially closely packed together in the trabeculae and the capsule. Both of these structures were consequently difficult to distinguish from the splenic pulp. About half of the nucleated red cells had definite sharp spherical nuclei, while the other half had irregular, shriveled pyknotic nuclei, often showing "clover leaf" or "budding yeast" shapes. Cells similar to these are found in any hyperplastic bone marrow, always mingled with the colonies of well preserved nucleated red cells. This shriveled appearance of the nucleus probably represents the initial stage of degeneration. Nearly all the nucleated red cells of both forms were extremely small and would be regarded as microblasts. In addition to the nucleated red cells there were moderate numbers of larger paler cells resembling megaloblasts, and occasional myelocytes. Hemosiderosis was well marked.

*Pancreas* The interlobular and interacinar connective tissue was moderately increased in amount and uniformly and heavily infiltrated with small nucleated red cells, together with moderate numbers of larger, earlier cells of the myeloid series (fig 10 A). An occasional eosinophil myelocyte was also seen. The connective tissue found in this organ and, in fact, in the other organs as well, showed definite abnormalities. The changes consisted in a swelling and hyalinization of the collagen fibrils which were collected into bands from 7 to 8 microns in width, in which the individual fibrils could not be distinguished. The significance of this alteration in the intercellular substance is not known.

*Liver* There was a considerable increase in the portal connective tissue, and this connective tissue was heavily infiltrated with small cells that, like those present in the other organs, were differentiating to erythroblasts. Rare eosinophil myelocytes were also present.

*Gastro-Intestinal Tract* Sections at various levels did not show any evidence of acute colitis. The submucosa and the adventitia showed a moderately heavy



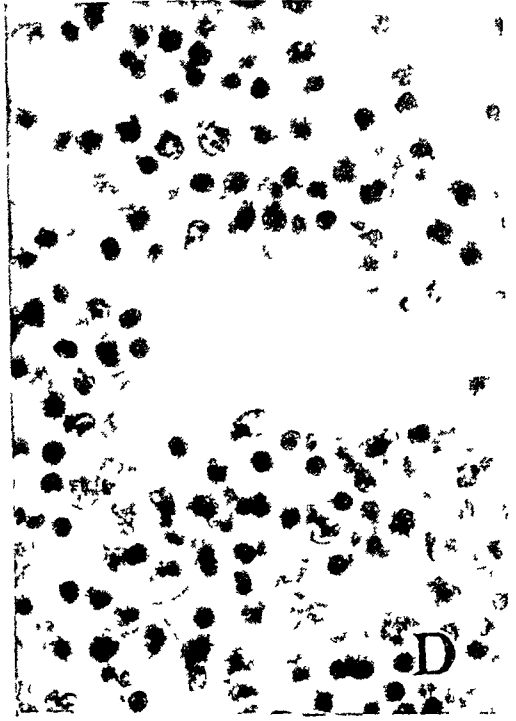


Fig 10 (case 6) —Aleukemic erythroblastosis *A*, a low magnification of the pancreas showing marked interlobular fibrosis and a tremendous accumulation of small dark cells, many of which are definitely erythroblasts, eosin-metheylen blue stain,  $\times 100$  *B*, an erythroblastic reaction in areolar tissue in the pelvis of the kidney. A cross-section of a large branch of the renal artery is shown in the lower left-hand corner, and a kidney tissue in the upper part of the field hematoxylin eosin stain,  $\times 40$  *C*, a low magnification of the vertebral marrow showing a preponderance of small, dark, nucleated red cells, eosin-methylene blue stain,  $\times 160$  *D*, a high magnification of a representative region in the marrow. About 80 per cent of the cells are nucleated red cells and most of them are small (microblasts), eosin-methylene blue stain,  $\times 1,000$

infiltration with the abnormal cells described Just beneath the peritoneum these cells were especially numerous

**Kidneys** Heavy infiltration was seen about the blood vessels, in the capsule and beneath the mucosa of the pelvis (fig 10 *B*)

**Lymph Nodes** The picture was similar to that observed in the spleen The capsules showed fibrosis and heavy cellular infiltration, which extended out into the surrounding areolar tissue (fig 12 *H*)

**Bone Marrow** The bone marrow (vertebral) appeared active, and again the great majority of the cells were nucleated red cells (fig 10 *C*), although granular myelocytes were more numerous than in the other organs Adult granulocytes were practically absent Many of the nuclei of the erythroblasts appeared to be naked, but, on careful examination, were seen to be surrounded by a clear space outlined as a faint cytoplasmic border Megaloblasts and normoblasts were about equally numerous (fig 10 *D*)

**Thymus** The picture was similar to that in the other organs, the capsule and the trabeculae showing a particularly heavy infiltration with definite erythroblasts

Sections of the other organs were essentially without abnormality

**Bacterial stains** Sections stained for bacteria showed a few diphtheroid bacilli on the capsular surface of the spleen and scattered organisms of a similar nature in the bone marrow No acid-fast rods or granules could be demonstrated

**Diagnosis**—Erythroblastic hyperplasia of the bone marrow, erythroblastic metaplasia of the mesenchymal tissue in the spleen, liver, kidneys, lymph nodes, pancreas, thymus, pericardium and peritoneum, fibrosis of the pancreas, liver and lymph nodes, low grade peritonitis of unknown origin, early acute bronchopneumonia, and erythroblastosis (acute aleukemic)

**CASE 7—History**—A boy, aged 6, entered the hospital complaining of weakness, pallor, perspiration and pain in the legs He had had whooping-cough at the age of 9 months and chickenpox at the age of 2 From the age of 10 months until two and one-half years before entry into the hospital, he had had frequent attacks of vomiting, sweating and weakness, with diarrhea (followed by constipation) lasting from seven to ten days and recurring about every three months

Following this he was well for six months, then (two years before entry) he complained of lameness and soreness in both knees This lasted for one month Except for pallor, he was then well until nine months before entry, then both ankles became lame and sore, but were not red or swollen One week later, he had an attack of acute tonsillitis Thereafter, his joints were intermittently lame, and on several occasions he had a fever of from 100 to 101 F for several days

**Examination and Course of the Disease**—The body was well developed and nourished but pale There was a slight thickening of the ankles, knees and elbows The examination of the blood showed marked anemia (a red cell count of from 2,300,000 to 1,400,000 with hemoglobin from 15 to 50 per cent) The white cell count during the period of observation varied from 5,800 to 1,130 The differential count showed from 60 to 72 per cent small mononuclear cells, which at first appeared to be myeloblasts but in subsequent smears appeared more like lymphocytes Reticulated red cells were numerous The blood was studied by an experienced hematologist, who, on the basis of the arthritis, leukopenia and relative lymphocytosis, thought the condition of the blood was secondary to a focus of infection with a toxic effect on the bone marrow Repeated transfusions gave only temporary relief After nine weeks' stay in the hospital, during which no focus of infection could be brought to light, tenderness developed over the left fourth and fifth ribs, anteriorly On exploration, osteomyelitis was found, and shortly

afterward hemolytic streptococci were grown from the blood stream. In spite of intravenous injection of mercurochrome-220 soluble, the patient died two days later. During the patient's stay in the hospital, the temperature ranged irregularly from normal to 104 F.

*Postmortem Examination*—Postmortem examination was made six hours after death. The body was well developed and nourished. There were abscesses in the marrow cavities of the fourth and fifth ribs, from which a streptococcus was cultivated. The mesenteric and the retroperitoneal lymph nodes were slightly enlarged. The lungs showed patchy bronchopneumonic consolidation. The spleen weighed 50 Gm. It appeared grossly normal. The entire colon showed an extreme thickening of the walls and a mucosa yellowish brown, with many irregular ulcerations having fibrous bases, often covered by a heavy membranous exudate. The left kidney showed a single small abscess with a contiguous area of infarction. Otherwise the kidneys appeared normal. The aorta showed acute atheromatous changes. The bone marrow in the femur, tibia and ribs was markedly hyperplastic and grayish red. It was firm and almost fibrous in some areas. The left kneejoint contained a glairy mucinous material and there was definite injection and roughening of the articular surfaces. The heart, pancreas, thymus, liver, gallbladder, suprarenal gland and brain did not show changes.

*Microscopic Examination*—Spleen. The reticular spaces showed prominent endothelium with frequent mitoses, and contained a few myelocytes and rare nucleated red cells, in addition to the usual cells. The malpighian corpuscles were rather small and widely separated. There was an extraordinary amount of hemosiderin present, and many of the red cells were stained yellowish or green.

Pancreas. Scattered collections of cells were seen in the interacinar connective tissue, the predominating cell being consistent in appearance with the early myeloblast.

Liver. The portal areas were crowded with these same cells (myeloblasts?) and a few similar cells were scattered through the sinusoids. The Kupffer cells were everywhere prominent and occasionally in mitosis.

Colon. The mucosal surface was covered with a thick layer of necrotic exudate, while the wall was cicatrized and fairly heavily infiltrated with inflammatory cells of all sorts, but adult polymorphonuclears were rare.

Lymph Nodes. The mesenteric lymph nodes showed a picture of chronic inflammation with a slight increase in the number of the cells resembling early myelocytes. Lymph follicles were entirely absent.

Kidneys. A section from the left kidney showed an acute abscess, typical in appearance, except for the fact that the polymorphonuclear leukocytes were few in number and often young in appearance. Other sections from both kidneys showed numerous intertubular and periglomerular aggregations of early myeloid cells similar to those described in the other organs (fig 11 A). Mitotic figures were frequent among these cells.

Bone Marrow. Sections of the marrow from the tibia, femur and ribs all showed marked hyperplasia. The marrow was almost uniformly composed of nongranular cells (fig 11 B), with only a few islands of erythroblasts and rare eosinophil myelocytes (fig 11 C). Adult polymorphonuclears were practically absent. Megakaryocytes were fairly numerous but atypical giant cells, like those seen in cases 1 and 2 were not observed. Mitotic figures were numerous. Many sections showed marked fibrosis. Sections of the other organs were essentially without abnormality.

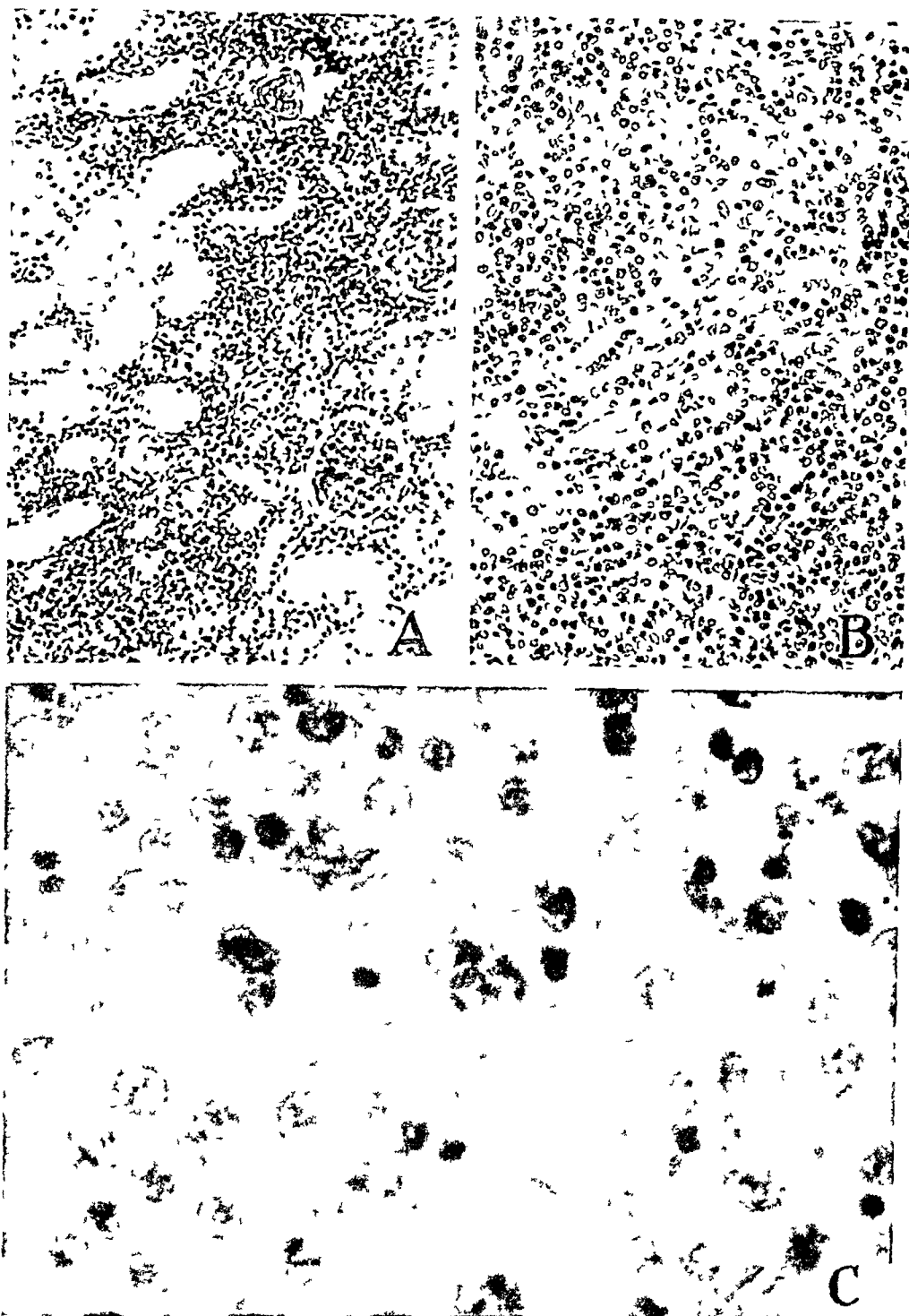


Fig 11 (case 7) —Prolonged sepsis with leukemoid changes A, a low magnification of the kidney showing leukemia-like aggregations of undifferentiated cells like those in the bone marrow Anatomically, the picture here is not distinguishable from that of true leukemia, eosin-methylene blue stain,  $\times 120$  B a low magnification of the marrow from the femur showing uniform cellularity almost without evidence of differentiation There is a slight fibrosis, eosin-methylene blue stain,  $\times 160$  C, a high magnification of the marrow showing a uniform replacement of the normal elements by primitive cells, eosin-methylene blue stain,  $\times 1,000$

**Bacterial Stains** In spite of the positive blood culture obtained forty-eight hours before death, bacteria could not be demonstrated in the sections, including those from the abscesses in the kidneys and the ribs

**Diagnosis**—Chronic ulcerative colitis, anemia (severe secondary), osteomyelitis of the ribs, septicemia, abscess of the left kidney (small), bronchopneumonia, marked hyperplasia and anaplasia of the bone marrow, myeloid metaplasia of the liver, kidneys and pancreas, chronic arthritis, and arteriosclerosis (acute)

**CASE 8—History**—A man, aged 52, entered the hospital complaining that he had suffered intermittent pain in the left upper quadrant of the abdomen for five

TABLE 1—*Summary of Clinical Features*

Case	Age	Sex	Duration	Fever	Purpura	Blood Picture	Other Clinical Features	Clinical Diagnosis
1	52	M	9 mo	Picket fence type	+	Severe anemia, leukopenia (4-6%), myelocytes (1-2%), nucleated reds	Joint pains, emaciation	Endocarditis?
2	61	M	9 mo	Irregular slight	++	Severe anemia, differential count normal, 10% normoblasts	Nutrition good, no response to liver diet	Primary anemia? aleukemic leukemia?
3	58	F	2 mo	Septic type	0	Severe anemia, leukopenia, relative lymphocytosis, few normoblasts	Nutrition good, herpes labialis	Acute primary anemia
4	16	F	4 mo	Moderate irregular	+++	Severe anemia, leukopenia, lymphocytosis, few normoblasts	Severe nose bleeds, vomiting, emaciation	Purpura hemorrhagica
5	3	M	9 mo	Slight, irregular	0	Severe anemia, leukopenia, lymphocytosis (relative)	No emaciation	Secondary anemia
6	7	M	2 mo	Slight, irregular	0	Moderate anemia, absolute lymphocytosis, 10% myeloblasts, many normoblasts	Severe diarrhea, emaciation	Ulcerative colitis
7	6	M	4 yr	Moderate, irregular	0	Severe anemia, leukopenia, lymphocytosis, (relative)	Joint pains, osteomyelitis, nutrition good	Secondary anemia
8	52	M	8 yr	Moderate, irregular	0	Severe anemia, leukopenia (4%), myelocytes (3%), nucleated reds	No emaciation, no free hydrochloric acid in stomach	Banti's disease? primary anemia?

years. He had previously been well except for typhoid fever at 21 years of age and an acute infection of the upper part of the respiratory tract at about the time the illness in question began.

**Examination and Course of the Disease**—Physical examination showed a yellowish pallor, a smooth tongue and an enormous spleen. There was moderate anemia (the red cell count being 3,128,000), and the color index was 1.2. The white cell count was 5,200, and the differential count was normal, except for the presence of 4 per cent myelocytes, 2 per cent myeloblasts and 156 normoblasts per cubic millimeter. Anisocytosis and poikilocytosis were marked. Gastric analysis did not show free hydrochloric acid.

The diagnosis of Banti's disease was made, although it was felt that it was difficult to rule out pernicious anemia and the hematologist was in favor of a diagnosis of aleukemic leukemia.

Splenectomy was done. The spleen weighed 1,403 Gm. Microscopically, the architecture was well preserved and there was marked erythropoietic activity. Nucleated red cells were numerous, but a still more striking feature was the presence of clusters of large cells with rounded, pale vesicular nuclei and bright blue staining, thready cytoplasm. These cells often occurred in what appeared to be syncytial masses. They were believed to be the immediate progenitors of the erythroblasts (erythrogenia). Other primitive cells (presumably myeloblasts) were fairly numerous. The diagnosis made was erythropoietic splenomegaly.

TABLE 2—*Summary of Pathologic Changes*

Case	Bone Marrow	Spleen	Lymph Nodes	Liver	Kidneys	Special Features	Pathologic Diagnosis
1	Ivory white, hyperplastic, anaplastic, giant cells	690 Gm myeloid metaplasia, giant cells	Slightly enlarged myeloid metaplasia, giant cells	2,190 Gm, diffuse myeloid metaplasia	Negative	Myeloid reaction in mesenteric fat and in peribronchial tissue	Aleukemic leukemia (myelogenous)
2	Red purple, hyperplastic, anaplastic	240 Gm, myeloid metaplasia	Not enlarged myeloid metaplasia	2,380 Gm leukemoid aggregations	Leukemoid aggregations	Myeloid reaction in peribronchial fatty tissue	Aleukemic leukemia (myelogenous)
3	Red, hyperplastic, anaplastic	520 Gm, increased cellularity	Not enlarged, increased cellularity	Not enlarged, leukemoid aggregations	Not enlarged, leukemoid aggregations	Small primitive cells, lymphoid?	Aleukemic leukemia (myeloblastic)
4	Hyperplastic, hemorrhagic, anaplastic	Normal size, increased cellularity	Slightly enlarged, increased cellularity	2,160 Gm, anatomically appeared to be leukemia	240 and 220 Gm, anatomically appeared to be leukemia	Myeloid reaction in pericardial fatty tissue	Aleukemic leukemia (myeloblastic)
5	Red, hyperplastic, anaplastic	Normal size, hematopoietic	Slightly enlarged hematopoietic	Negative	Not enlarged, leukemoid aggregations	Fatty infiltration of viscera	Aleukemic leukemia (myeloblastic)
6	Red, hyperplastic (erythroblastic)	Slightly enlarged nucleated red cells, fibrosis	Slightly enlarged, nucleated red cells, fibrosis	Fibrosis, erythroblasts	Nucleated red cells, especially in pelvis	Fibrosis and erythroblasts in pancreas	Aleukemic erythroblastosis
7	Grayish red, hyperplastic, anaplastic	Normal size, slightly hematopoietic	Slightly enlarged, slightly hematopoietic	Portal leukemoid aggregations	Leukemoid cellular aggregations	Primitive cells in pancreas	Sepsis, with leukemoid changes
8	Autopsy not done. Developed blood picture typical of myelogenous leukemia. Surgically removed spleen showed hematopoietic activity.						

Following the operation, there was a continuous mild afternoon fever, in spite of which the patient eventually went home and got along fairly well for a time. The blood picture was observed from time to time during the five months that followed. There was not any change except for a slight temporary improvement in the red count.

Two and one-half years after the operation, the patient returned to the hospital. The afternoon fever was still present. The red cell count was 2,010,000, and the white cell count 180,000, with 83 per cent myelocytes. With radiation the white cell count fell to 8,000, but the patient lived only one month longer. Necropsy was not done.

## COMMENT

*Aleukemic Leukemia*—The five cases described and classified here as aleukemic leukemia showed great diversity from the clinical point of view. They had in common, however, the occurrence of an unexplained severe progressive anemia.

Pathologically, they showed much similarity to one another, the outstanding features being hyperplasia and marked anaplasia of the bone-marrow, with leukemia-like cellular aggregations of various magnitudes in the various organs. The cells in the visceral aggregations always corresponded closely to those in the marrow.

The anemia in cases of typical leukemia is usually considered to be secondary to leukemic "infiltration" of the bone marrow. On the other hand, Helley<sup>20</sup> and others believed that changes anatomically resembling those of leukemia may develop in association with certain types of severe anemia. The older term *leukanemia*, implying as it did an idiopathic anemia with leukemoid manifestations, is, after all, perhaps, the best name that has been proposed for many of these conditions. Steinberg<sup>7</sup> suggested that certain cases, being more closely related to the leukemias (as case 5 of this series), would be more appropriately termed *anemo-leukemia*.

In view of the probably neoplastic nature of the true leukemias, about which there is almost universal agreement, it would seem important to draw a sharp line between true leukemia and other, nonneoplastic conditions that are morphologically similar. The difficulty of drawing this line definitely is well brought out by the cases presented. It may be said that, from the anatomic point of view, the relation to true leukemia is quite definite in case 5, somewhat doubtful in cases 1 and 2 and still more doubtful in cases 3 and 4.

Concerning the etiology and nosology of aleukemic leukemia, there is a great difference of opinion. Many pathologists refuse to accept the term, denying the existence of the problem. Lazarus<sup>21</sup> believed that some cases of pernicious anemia and some cases of leukemia, because of certain deviations from the usual picture, are to be labeled with this term. Sternberg<sup>22</sup> believed that these conditions have much in common with the so-called acute leukemias, which he regarded as entirely different from true (chronic) leukemia, considering them to be severe generalized infections with a peculiar reaction on the part of the hematopoietic system. Naegeli,<sup>23</sup> similarly, believed that most cases of aleukemic leukemia are primarily severe anemias of infectious origin.

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20 Helley, K. in Henke and Lubarsch. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 2, p. 1035.

21 Lazarus, cited by Sternberg, footnote 7, p. 56.

22 Sternberg, footnote 7, p. 57.

23 Naegeli, cited by Sternberg, footnote 7, p. 57.

The explanation of certain of the cases of so-called aleukemic leukemia as being caused by infections is to a certain extent supported by several facts brought out in the series of cases described here. In the first place, the clinical pictures, particularly, in cases 1 and 3, were certainly suggestive of infection. The failure to obtain a positive blood culture does not by any means rule out this possibility. The finding of bacteria in the lesions of the kidney in case 5 and in the blood vessels in case 4 lends some support to this conception. Finally, the similarity of the anatomic changes in case 7 (prolonged bacterial intoxication with terminal streptococcus septicemia) to the changes in the cases classified as aleukemic leukemia, strongly suggests that the etiologic factors may be fundamentally similar.

The possibly close relation of some of these conditions to pernicious anemia is strongly suggested by cases 2 and 3. In these cases, the anemia was definitely of the "pernicious" type. In both cases, the general state of nutrition was well maintained. If the bone marrow in these cases is compared with that in pernicious anemia, the principal difference seems to be that in cases 2 and 3 early undifferentiated elements are present to the almost complete exclusion of differentiated elements. Peabody,<sup>24</sup> studying the marrow during life from cases of pernicious anemia, showed that relapses are characterized by an increase in the number of primitive cells (megaloblasts), while during remissions the more differentiated cells (erythroblasts) make their appearance. It seems not improbable that, in cases of pernicious anemia running an acute course without remissions, extreme anaplasia of the bone marrow may develop, giving a picture similar to that in cases 2 and 3.

The position of many of these conditions apparently intermediate between pernicious anemia and leukemia has led to the belief that these two conditions may be etiologically in close relationship, their differences being due to variations in the chemical nature and the concentration of the toxic factor or to the individual predisposition. Such a hypothesis was advanced by Ellerman,<sup>12</sup> who, by inoculation of the virus of fowl leukosis in hens, was able to produce a variety of conditions varying from one resembling pernicious anemia through "aleukemic" leukemia to true leukemia. Once established in an individual fowl the type of condition produced always remained constant.

The hematologic classification of these five cases offers great difficulty. Cases 1 and 2 are regarded as definitely of the myelogenous type, for while the majority of the cells in the bone marrow and the other organs were early and undifferentiated in appearance, there was in both cases a plentiful sprinkling of definite myelocytes.

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<sup>24</sup> Peabody, F. W. The Pathology of the Bone Marrow in Pernicious Anemia, *Am J Path* **3** 179, 1927.



Cases 3, 4 and 5, because of the absence of definite myeloid characteristics, were at first regarded as possibly of lymphoid origin. Generalized enlargement of the lymph nodes and hyperplasia of the lymph follicles in the lymph nodes and in the spleen were not striking in any of these cases. It is unfortunate that the blood smears made during life were discarded, and that attempts to apply various modifications of the oxidase stain to old formaldehyde-fixed material were not successful. Opinions differ greatly, however, as to the value of the oxidase method in such cases. It seems fairly well established that there is a completely nongranular precursor of the myelocyte, which strikingly resembles the various cells of the lymphocytic series. Several German workers (among them Schilling<sup>25</sup>) stated that these cells often give a positive oxidase reaction in spite of their nongranular character, while Jolly<sup>26</sup> and others found these cells oxidase-negative.

If one believes with Maximow<sup>27</sup> and others that the lymphocyte is an undifferentiated cell identical with the hematocytoblast or earliest blood cell, the separation of undifferentiated cell leukemias into lymphatic and myelogenous types becomes unimportant.

Ellerman,<sup>12</sup> working with fowl leukosis, described an "intravascular lymphoid leukosis" in which the type cell markedly resembled a lymphocyte but was regarded by him as the progenitor of the erythroblast. This condition, which was characterized by severe anemia, he designated "erythroleucosis." It must be admitted that there is not a positive method of distinguishing in fixed tissues between the myeloblast and the early megaloblast. The severe anemia in the cases reported here and the almost complete absence of adult granulocytes in the marrow suggest that the erythropoietic tissue rather than the leukopoietic tissue is primarily involved. An attempt was made to substantiate this conception by measuring the angles of mitosis of the primitive cells, Ellerman and Petri<sup>28</sup> believing that the angle for the myeloblast is 60 degrees, and the angle for the erythrogonium is 20. Although mitoses were frequent in all the marrows, spindles were rarely found and the material appeared to be unsuitable for a study of this nature.

Careful work led Cunningham, Sabin and Doan<sup>29</sup> to the belief that endothelium gives rise to megaloblasts and the red cell series, while the

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25 Schilling, V. *Das Blutbild*, ed 2, Jena, Gustav Fischer, 1922, pp 70 and 119.

26 Jolly, J. *Traite technique d'hematologie, morphologie, histogenese, histophysiologie, histopathologie*, Paris, A. Maloine et fils, 1923, p 370.

27 Maximow, A. *Morphology of Mesenchymal Reactions*, Arch Path 4:557 (Oct) 1927.

28 Petri, S. *Histologische Untersuchung eines Falles von myeloischer Leukämie mit messung der Mitosenwinkel* Folia Haemat Arch 32:103, 1926.

29 Cunningham, R., Sabin, F., and Doan, C. *The Development of Leukocytes, Lymphocytes, and Monocytes from a Specific Stem Cell in Adult Tissue*, Contrib Embryol 82, Carnegie Inst., Washington 16:227, 1925.

reticular cell gives rise to myeloblasts, monoblasts and, at times, lymphoblasts. Other workers,<sup>27</sup> however, postulated a common stem cell for both the erythrocytic and the granulocytic series. Even if it is assumed that the red cells normally come from endothelium, it is possible that, under pathologic conditions, reticulum cells also are their ancestors.

In the present state of our knowledge, it must be admitted that instances of atypical leukemia occur in which the type cell cannot be classified as a lymphocyte or an early myeloblast or megaloblast with any degree of certainty, even with the help of the oxidase reaction.

Steinberg<sup>21</sup> believed that practically all cases of acute leukemia are myelogenous in type, those that have been regarded as of lymphocytic origin being simply cases in which the type cell is primitive and consequently of a lymphoid appearance. The supravital technic of staining offers a possible method of approach to this question.

As has been stated, the essential pathology of the marrow in the cases reported here is the replacement of differentiated elements by primitive cells. In secondary anemias and in leukocytosis one finds this process of anaplasia in a slight degree only, the reversion in cases of erythropoiesis being principally from the adult red cell to the erythroblast, and in cases of leukopoiesis from the adult granulocyte to the late myelocyte. The occurrence of early cells (megaloblasts and myeloblasts) in the marrow in large numbers is generally characteristic of the more severe disorders of the blood (pernicious anemia and myelogenous leukemia).

The anaplasia in the cases reported here is more complete than that found in either pernicious anemia or the true leukemias, and it seems probable that in these cases the majority of the cells in the marrow that have been classified as early myeloblasts or megaloblasts are in reality only slightly more differentiated than the reticular cells or the endothelial cells.

The appearance of the cells composing the visceral aggregations in these cases (especially case 3) strongly supports the belief that the blood cells may, under abnormal conditions, be formed directly from undifferentiated mesenchymal elements, variously known as adventitial cells (Marchand), clasmatoocytes (Ranvier), polyblasts (Ziegler) and hemato-histioblasts (Ferrata).

The peculiar gigantic cells that were so numerous in the bone marrow and other organs in cases 1 and 2 deserve special mention. Apparently similar cells have been reported as the outstanding feature in certain rare cases of true leukemia (Schwarz,<sup>30</sup> Himbdenberg,<sup>30</sup> Barth,<sup>30</sup> Koerner<sup>30</sup>),

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30 Schwarz, Himbdenberg, Barth, Koerner, cases summarized by Lubarsch in Henke and Lubarsch. *Handbuch der speziellen pathologischen Anatomie und Histologie*. Berlin, Julius Springer, 1926 vol 2, p 658.

and of aleukemic leukemia (Firket and Campos<sup>31</sup>) These cells have been variously regarded as true megakaryocytes (Koerner<sup>30</sup>) and as hypertrophic early blood-forming cells (Barth<sup>30</sup>) Jaffe<sup>17</sup> gave the latter interpretation to similar large cells that were present in smaller numbers in his cases of "aleukemic myelosis"

The article by Firket and Campos<sup>31</sup> is of particular interest These workers reported a case in which gigantic cells were the outstanding feature of the visceral changes The blood picture was aleukemic and the bone marrow aplastic (fatty) Previous exposure to benzol was a possible etiologic factor By the intravenous injection of saponin in rabbits, these workers were able to produce a generalized myeloid metaplasia, in which large cells (regarded as megakaryocytes) were the outstanding feature Their interpretation is that saponin has a particularly destructive action on the blood platelets, leading to regenerative hyperplasia of the megakaryocytes They minimize the resemblance of the experimentally produced lesion to that in the reported case, chiefly because the bone marrow in the latter was fatty The changes that they produced by the injection of saponin certainly resemble markedly, from an anatomic standpoint, the changes present in the organs of the patient in case 1 of this series It would seem worth while to carry out further work along these lines, using various toxic and hemolytic substances, including bacterial toxins

*Erythroblastosis*—The justification for applying this term to case 6 is that the latter appears to be a case of an atypical leukemoid condition in which the bone marrow is hyperplastic, differentiation being apparently arrested at the stage of the erythroblast The presence of large numbers of nucleated red cells in the mesenchymal tissue of nearly all the organs seems best explained as a myeloid, or rather erythroblastic metaplasia

The term fetal erythroblastosis has been applied (Eichelbaum<sup>32</sup>) to a condition occurring in newly born infants, practically always in association with congenital edema The anatomic changes in such cases seem to be merely an exaggeration of the extramedullary hematopoietic activity frequently noticed at birth (especially in association with congenital syphilis) The occurrence of a similar condition in older children or adults has not, as far as can be learned, been previously reported

Erythroblastoma (localized tumor-like masses of erythroblastic tissue, usually in the bone marrow) is a rare but well recognized condition, and similar tumor-like masses have been reported in the suprarenal

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31 Firket, J, and Campos, E Generalized Megakaryocyte Reactions to Saponin Poisoning, Bull Johns Hopkins Hosp **33** 271, 1922

32 Eichelbaum Hydrops congenitus, Arch f Gynak **119** 149, 1923

gland (Mieremet<sup>33</sup>) In a case reported recently (Warren<sup>34</sup>), diffuse tumor-like masses were present in the pelvises of both kidneys, while the liver and the other organs showed striking leukemoid changes In a case observed at the Peter Bent Brigham Hospital (not yet reported) in which there was marked splenomegaly, a pyelogram revealed the presence of a renal or retroperitoneal tumor mass in the region of the right kidney An excised cervical node showed extreme hematopoietic activity with many large islands of nucleated red cells and marked fibrosis and distortion of the architecture This patient died A necropsy was not obtained

These observations may indicate that in the erythroblastic tissue, as well as in the leukoblastic and lymphoblastic tissue, intermediate types of disease may be found ranging from localized neoplasm to leukemia-like conditions From this point of view, it seems proper to classify case 6 as aleukemic erythroblastosis (corresponding to aleukemic myelosis and lymphadenosis)

*Leukemoid Conditions Secondary to Infection*—The blood in acute infections may undergo extraordinary changes in its composition, from the leukopenia of typhoid fever and the lymphocytosis of certain acute infections to a polymorphonuclear leukocytosis with a white count exceeding 200,000 These changes, of course, represent the normal functioning of the defense mechanism against bacterial invasion

The alteration produced in the blood-forming tissues in these infections is a simple hyperplasia, differentiation being chiefly in the direction of that type of blood cell that is being most actively destroyed On recovery from the infection there is a rapid return to the normal condition in the bone marrow The hyperplasia is, as a rule, confined to the bone marrow, although in certain cases of chronic infection a slight myeloid activity may be found in the spleen

In certain infectious processes, notably infectious mononucleosis<sup>15</sup> and agranulocytic angina,<sup>16</sup> more profound alterations are to be found in the circulating blood These two conditions bear a certain resemblance to each other Necrotic lesions of the mouth and the tonsils are common to both In agranulocytosis there is leukopenia, with a marked decrease in the circulating granulocytes, while in mononucleosis there is a variable lymphocytic (?) leukocytosis Agranulocytosis is usually fatal, while mononucleosis is never fatal In certain cases described in the literature as agranulocytosis (Krumbhaar,<sup>8</sup> Moore and Wieder<sup>35</sup>)

33 Mieremet, C W G Ein aus dem verschiedenen Elementen des Knochenmarks bestehender Tumor in der Nebenniere, *Centralbl f allg Path u path Anat* **30** 403, 1919

34 Warren, S Malignant Tumor Simulating Bone Marrow, *Am J Path* **4** 51, 1928

35 Moore, J A, and Wieder, H S Agranulocytic Angina, Report of a Case with Two Attacks, *J A M A* **85** 512 (Aug 15) 1925

there was only a mild leukopenia, and these cases frequently recover. Such cases as these greatly resemble infectious mononucleosis, the only difference being that the abnormal cells have been regarded as myeloblasts instead of lymphocytes or monocytes. Thus, the mild cases of agranulocytosis resemble infectious mononucleosis, while the fatal cases are remarkably similar to the so-called acute leukemia.

Reports of postmortem examinations in cases of infectious mononucleosis are not to be found in the literature (because of its invariably favorable termination), so that we are left in the dark regarding the occurrence of leukemia-like visceral changes in this condition. Excised lymph nodes<sup>15</sup> usually show hyperplasia, an increased cellularity (atypical mononuclear cells being numerous) and a few eosinophils—in short, little more than one might see in a lymph node draining an area of sepsis.

Postmortem examinations in cases of agranulocytosis are also rare. Sternberg<sup>11</sup> reported a case in which stomatitis was present, with marked leukopenia and a relative lymphocytosis. This patient died with streptococcus septicemia. At autopsy, the bone marrow was found cellular, being composed chiefly of "round" cells that were oxidase-negative. The kidneys and the liver showed moderate cellular aggregations, which, as far as can be learned from the description, were of about the same order of magnitude as those seen in case 7 of this series. Sternberg regarded this case as one of acute leukemia.

Krumbhaar<sup>8</sup> also reported a case of severe gastrocolitis in which streptococcus septicemia developed shortly before death. Two days before death there was a polymorphonuclear leukocytosis. On the day before death, the white count was 69,000, with 55 per cent atypical mononuclear cells that were apparently myeloblasts. At autopsy, leukemia-like collections of similar cells in the various organs were sufficiently striking to raise seriously the question whether the condition might be acute leukemia. He was inclined to regard it, however, as an abnormal response of the hematopoietic system to infection. It is to be noted that this is Sternberg's definition of acute leukemia.

Nyiri<sup>36</sup> reported a case in which there was fever, stomatitis and a white count of 7,700, with 34.2 per cent of "unripe" myeloid elements. A hemolytic staphylococcus was recovered from the blood stream, but the patient made a complete recovery.

The similarity of the picture in the kidneys in cases 5 and 7 to that of the so-called acute nonsuppurative interstitial nephritis, is perhaps worth mentioning. In this latter condition, which is observed chiefly in children that have died of diphtheria or scarlet fever, the kidney may be

quadrupled in weight (Councilman<sup>37</sup>), with tremendous accumulations of cells between the tubules and around the glomeruli and blood vessels. These cells appear to be partly of the lymphoid series, partly plasma cells and partly atypical mononuclear cells, with a variable but often insignificant number of polymorphonuclear leukocytes. The small amount of degenerative change has been regarded as secondary to the cellular aggregations, rather than as the cause of them. Accumulations of cells similar to but less striking than those found in the kidneys have been described as occurring in the heart, bone marrow, spleen and liver in these cases. The term acute lymphomatous nephritis has been applied to the condition.

The origin of these cells has been in dispute. Mitotic figures are frequent among them, and they multiply largely in situ. Various workers have suggested their possible local origin from undifferentiated mesenchymal elements. Von Mollendorff<sup>38</sup> and his followers recently became convinced that the various cells that appear in the tissues in response to inflammation (including the polymorphonuclear leukocytes) have a local origin. Although the evidence that these workers presented by no means overthrows the well established belief that the origin of the polymorphonuclears in acute inflammation is in the bone marrow, it is possible that the local metaplastic origin of blood cells may become of importance under certain conditions.

The anatomic observations in these cases of nonsuppurative interstitial nephritis do not differ materially from those of many cases of so-called aleukemic leukemia, and if one were not aware of the underlying cause (acute infection) there would be serious danger of confusing the two conditions.

*Leukemoid Conditions Secondary to Other Destructive Lesions of the Blood and the Hematopoietic System*—There is some evidence that true leukemia may at times develop on the basis of a preexisting hyperplasia of the hematopoietic system. Case 8 of this series, in which an unknown type of "splenic anemia" eventually presented itself as myelogenous leukemia, is almost duplicated by a case in the series reported by Krumbhaar.<sup>8</sup> Cases have been reported in which true myelogenous leukemia was superimposed on a picture of prolonged severe anemia of malarial origin (Decastello<sup>39</sup>). The frequent occurrence of leukemoid blood pictures and the occasional development of

37 Councilman, W. T. Acute Interstitial Nephritis, *J. Exper. Med.* **3** 393, 1898.

38 Von Mollendorff, W. Die örtliche Zellbildung in Gefasswänden und im Bindegewebe, *München med. Wchnschr.* **73** 135, 1927.

39 Decastello. Acute Leukaemie und Sepsis, *Wien Arch. f. inn. Med.* **11** 217, 1925.

true myelogenous leukemia in cases of erythremia was stressed by Minot<sup>40</sup> and others

In pernicious anemia the regenerative hyperplasia usually stays within normal bounds, but myeloid changes may be found in the spleen, liver and lymph nodes, the frequency being in the order mentioned. Myelogenous leukemia has been reported as developing in cases of pernicious anemia, but Jaffe<sup>17</sup> suggested that such cases may initially have been "aleukemic myelosis."

Myeloid metaplasia may occur in the liver and the spleen in cases in which the bone marrow has been destroyed by metastatic carcinoma (McCallum<sup>41</sup>), and the same picture is seen in certain cases of osteosclerotic anemia. Sternberg<sup>11</sup> believed that these changes are in most cases secondary to marrow fibrosis from various causes, although in rare cases the fibrosis may be secondary to leukemia.

On the whole, the development of leukemoid conditions and true leukemia on the basis of regenerative hyperplasia of the hematopoietic system appears to be about as frequent as the development of benign and malignant neoplasms following functional or regenerative hyperplasia of epithelial tissues.

#### CONCLUSIONS

Five cases of "aleukemic leukemia" are reported which show a general pathologic similarity but a striking clinical diversity. Anatomically, the outstanding features of these cases were hyperplasia and extreme anaplasia of the bone marrow, and the presence in the viscera of foci of early myeloid cells, which probably originated largely by metaplasia from undifferentiated mesenchymal elements. These anatomic changes are not pathognomonic of "aleukemic leukemia," since a similar picture may be produced by prolonged sepsis (either because of destruction of the blood or through toxic action on the marrow).

In such extremely anaplastic marrow, the majority of the cells show so little evidence of differentiation that it is not always possible to determine whether the hyperplasia is primarily leukoblastic, erythroblastic or lymphoblastic.

Clinically, the only constant fact in these cases was severe anemia. The clinical pictures and pathologic changes lend considerable support to the view that many of these conditions are primarily severe anemias of infectious or toxic origin with atypical regenerative hyperplasia of the hematopoietic system. This point of view is further strengthened by case 7, in which similar leukemia-like visceral aggregations developed, apparently secondary to a severe anemia accompanying prolonged sepsis.

40 Minot, J. R., and Buckman, T. E. Erythremia, *Am J M Sc* **166** 469, 1923.

41 McCallum, W. G. *Textbook of Pathology*, ed. 2, Philadelphia, W. B. Saunders Company, 1920.

A similarity is pointed out between certain cases of subleukemic visceral myeloid metaplasia and the so-called "acute nonsuppurative interstitial nephritis"

One case of acute aleukemic erythroblastosis is reported that appears to be unique in the literature, and one case in which the picture of myelogenous leukemia was superimposed on that of a "splenic anemia" of several years' duration

Some evidence is presented for the belief that leukemoid conditions and even true leukemia may at times develop on the basis of a pre-existing nonspecific hyperplasia of the blood-forming tissue

#### EXPLANATION OF FIGURE 12

Fig 12—The sections *A* to *G* present representative cells from the bone marrow of cases 1 to 7. The cells shown for each case are of the type that greatly predominate (from 90 to 98 per cent). The drawings were all made at a constant magnification

*A* (case 1) Eosin-methylene blue stain. Hyperplastic, primitive, blood-forming cells, frequently multinucleated. The relation of the cells to the intercellular substance may be noted

*B* (case 2) Eosin-methylene blue stain. The cell in the upper left corner is probably an early megaloblast, while the other cells correspond to early myeloblasts or "primitive free cells"

*C* (case 3) Hematoxylin eosin stain. The indentation and lobulation of the nuclei may be noted. These cells are probably derived from the reticulum cells, one of which is shown in the center of the figure

*D* (case 4) Eosin-methylene blue stain. The two large cells are probably early megaloblasts, the others early myeloblasts

*E* (case 5) Eosin-methylene blue stain. The nuclei are small, hyperchromatic and frequently lobulated. The large cell is probably a hypertrophic reticulum cell

*F* (case 6) Hematoxylin eosin stain. Erythroblasts are shown, many of which have lobulated and shriveled nuclei. Two megaloblasts are present

*G* (case 7) Giemsa stain. Although stained somewhat differently, these cells are comparable to those in the marrow of cases 2 and 4 (*B* and *D*)

*H* (case 6) Erythroblastic metaplasia of loose areolar tissue of the mesentery, about 2 mm distant from the capsule of a small lymph node. Eosin-methylene blue stain. Most of the cells are erythroblasts, but a few reticulum cells and intermediate stages are shown. It may be noted that the erythroblasts are extravascular. In the right lower quadrant is a large erythroblast (in mitosis?) and to the right of this cell is a basophil cell (megaloblast?) which is beginning to accumulate hemoglobin



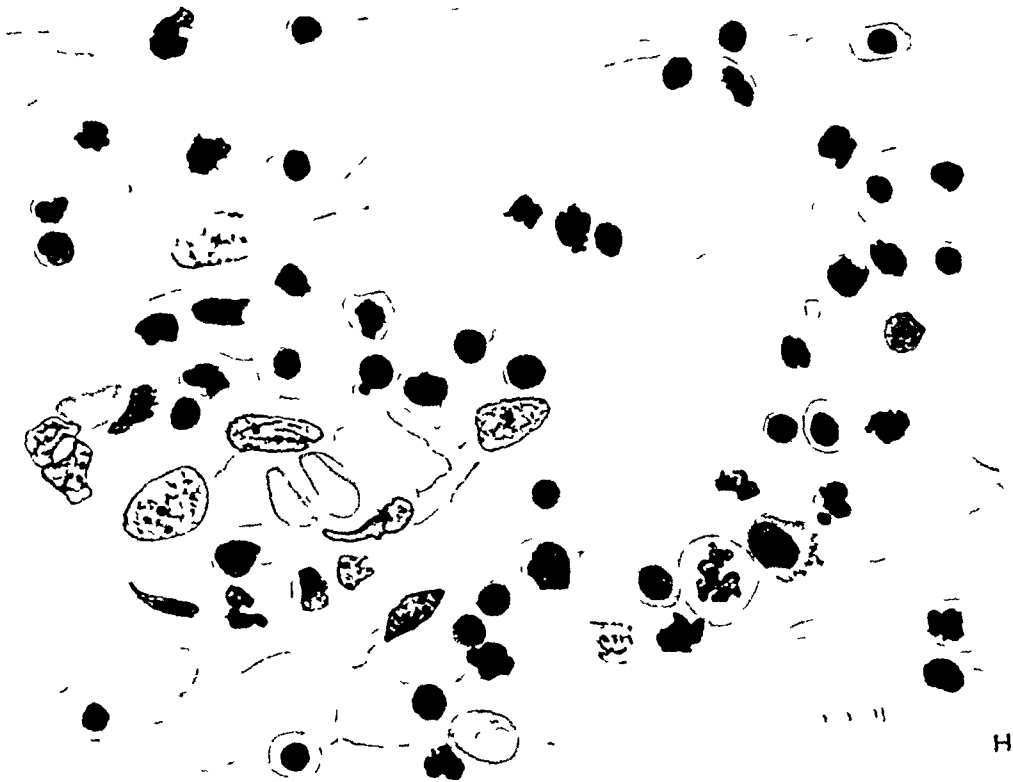
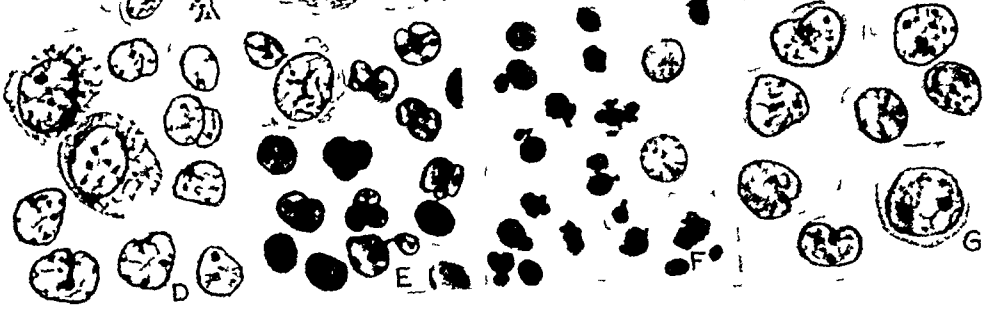
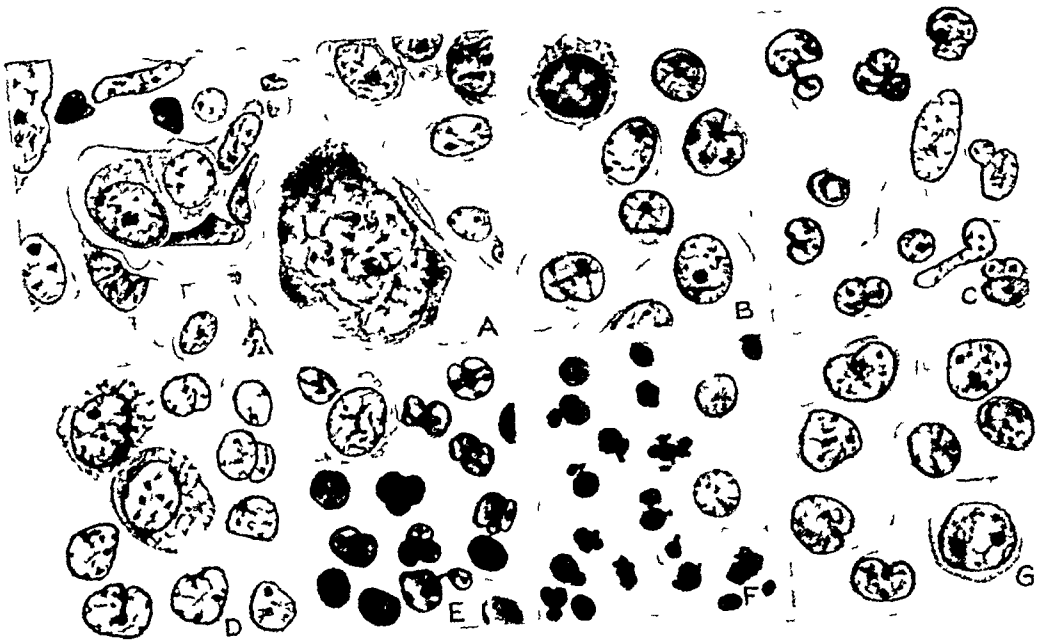


Figure 12



# CERTAIN EFFECTS OCCASIONED IN DOGS BY DIPHTHERIA TOXIN

I \* A REPORT OF THE VISCERAL LESIONS \*

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In the course of experiments in another connection, I had occasion to inject diphtheria toxin intravenously into the circulation of normal dogs. Some of the results were so striking that I have decided to add them to the literature dealing with the pathologic changes resulting from the injection of diphtheria toxin. The experiments are of interest both to the clinician and to the pathologist. In this paper, I present certain effects of the injection of diphtheria toxin on the heart observed while the animals were living, as well as the gross and microscopic observations at autopsy. In a second paper, I shall describe the changes that took place in the size of the heart, and give other data connected with the occurrence of these changes.

## MATERIAL AND METHOD

Mongrel dogs of widely differing weights were used. The diphtheria toxin was obtained from the New York City Board of Health. It was injected intravenously in the ear. The minimal lethal dose for guinea-pigs was 0.00125 cc. As one lot of the toxin was sufficient for the series of experiments, its strength was approximately constant. The toxin was diluted with sterile physiologic sodium chloride solution. Not finding any mention in the literature of the minimal lethal dose of diphtheria toxin for dogs, I roughly calculated a dose based on the ratio of the weight of the dog to the weight of the guinea-pig. Since I did not wish the animals to die too soon after the injection, in the first experiments I injected a dose per kilogram of body weight that I estimated would prove fatal within several days. In later experiments, I tested within narrow limits the amount of toxin per kilogram of body weight that would be followed by a fatal outcome.

During the course of these experiments, roentgenograms of the heart and electrocardiograms were taken almost daily. Records of the body weight were made at the same time. In some cases, the urine was tested for albumin and examined microscopically. Because of jaundice, the urine and the blood plasma were examined for bile pigments. At autopsy, the material was examined in the gross, and sections of the organs were taken for microscopic study.

The hearts, at autopsy, after the removal of blood clots, were fixed whole in 10 per cent formaldehyde solution. The method of fixation and preparation for section was that described by Lewis<sup>1</sup>. The separation of the fixed heart into the

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\* From the Hospital of the Rockefeller Institute for Medical Research

<sup>1</sup> Lewis, T. Observations upon Ventricular Hypertrophy with Especial Reference to Preponderance of One or the Other Chamber, *Heart* 5 367, 1913-1914

right and the left ventricles was carried out according to a method devised by Herrmann and Wilson<sup>2</sup> These were weighed, and the ratio of the weight of the right ventricle to that of the left ventricle (called here the L/R ratio) and the ratio of the combined weights of both ventricles to the body weight ( $\frac{L+R}{B+W}$ ) were calculated

The dogs were divided into groups 1 and 2, group 2 being subdivided into groups A, B and C,<sup>3</sup> the basis of the division being the amount of toxin injected per kilogram of body weight, decreasing amounts being given in the succeeding groups

#### OBSERVATIONS FOLLOWING THE INJECTIONS

*Course and Autopsy*—GROUP 1—The four dogs in this group (nos 81, 82, 83 and 84 of table 1) received approximately the same amount each of toxin per kilogram of body weight, given in two doses varying from 0.00161 to 0.00232 cc for the first dose and from 0.00105 to 0.00168 cc for the second dose, the total being from 0.00327 to 0.00337 cc The interval of time between the two doses varied from two to four days Following the injections the dogs became ill, ate little and lost weight, they died from three to five days after the first injection Three dogs (nos 81, 82 and 83) developed marked jaundice of the skin and the sclerae, which was at a maximal intensity at the time of death At autopsy, the skin and the subcutaneous tissues were stained an intense yellow, as were also the membrane lining the pleural cavity, the pericardial fat and the large blood vessels There were ecchymoses in the subcutaneous tissues, along the intercostal blood vessels, in the pericardial fat, sometimes in the visceral pericardium, in the kidney capsule and often in the cortex of the kidney The lungs from two animals showed large areas of consolidation and in one instance marked edema

GROUP 2 A—Nine dogs (nos 85, 86, 87, 97, 99, 102, 103, 104 and 105 of table 2) received each, in a single injection, 0.00168 cc of toxin per kilogram of body weight These dogs showed the same objective symptoms as the animals in group 1, and died from two and a half to five days after the injection Eight developed marked jaundice of the skin, which in some of the animals, appeared only shortly before death The gross observations at autopsy did not differ from those made in the dogs belonging to group 1 Dog 104 lived for two and a half days following the injection of the toxin, it did not show any jaundice but ecchymoses were present at autopsy Dog 85 moved during the injection, so that about half of the dose of toxin was given subcutaneously This dog lived for eight days after the injection, but showed the same clinical course as the other dogs of this group, including jaundice and gross lesions at autopsy

GROUP 2 B—Six dogs (nos 107, 108, 109, 110, 111 and 112 of table 3) were each given, in one injection, 0.00135 cc of toxin per kilogram of body weight These did not become so acutely ill as the animals receiving the larger doses, they lost weight and died from four to nineteen days after the injection of toxin Paralysis of the limbs were occasionally seen in these animals Only one dog (no 108) developed jaundice and showed ecchymoses at autopsy

GROUP 2 C—Five dogs (nos 88, 89, 90, 101 and 106 of table 4) received each, in one injection, 0.001 cc of toxin per kilogram of body weight Four did not

2 Herrmann, G. R., and Wilson, F. N. Ventricular Hypertrophy. A Comparison of Electrocardiographic and Postmortem Observations, *Heart* 9:91, 1922

3 Group 2 is subdivided in this manner in order that this paper may agree, in arrangement of the material, with the second paper of this series

TABLE 1—Summary of the Clinical and Postmortem Observations in the Dogs of Group 1

Dogs, Sex	Weight, kg	Toxin per kilogram of Body Weight		Day of Death After Injection	Leech moses at Au- topsy	Summary of Microscopic Observations				Electro- cardio- gram R <sub>2</sub> and R <sub>3</sub> decreased	L/R Ratio 1.38	L + R B W		Ratio Initial Body Weight Autopsy 0.00572
		First Dose, Cc	Second Dose, Cc			Heart	Lungs	Liver	Kidneys			Spleen	Initial Body Weight	
S1 ♀	10.75	0.00232	0.00105	2	+	One small area of leukocytic infiltration	Broncho- pneu- monia, small abscesses	Central ne- crosis, phagocy- tosis by Kupfer cells, nests of round cells and cells resem- bling nu- cleated red cells	Necrosis of tubu- lar epi- thelium, nuclei not seen in these areas	R <sub>2</sub> and R <sub>3</sub> decreased	1.38	0.00483	0.00572	
S2 ♀	12.45	0.00161	0.00166	4	+	One small area of leukocytic infiltration	Patho- logic lesions not seen	Central necrosis, bile throm- bi, phago- cytosis, clumps of round cells with cells resembling nucleated red cells	Many tubular epithelial cells with out nuclei, bile stained casts	R <sub>2</sub> and R <sub>3</sub> decreased	1.25	0.00698	0.00874	
S3 ♂	7.95	0.00166	0.00166	2	+	A few red cells, B a few red cells, C small areas of round cell infiltration, D normal	Pneumonia	Central necrosis, bile throm- bi, phago- cytosis, clumps of round cells and cells resembling nucleated red cells	0	No change	1.21	0.00656	0.00702	
S4 ♂	8.91	0.00168	0.00168	2	+	Small area in which muscle fibers are replaced by fibrous tissue	Conges- tion	Central necrosis, necrotic areas with red cells, clumps of round cells and cells resembling nucleated red cells	Necrosis of tubules, red cells between tubules, collections of round cells, and cells resembling nucleated red cells (?)	R <sub>2</sub> and R <sub>3</sub> decreased	1.24	0.00472	0.00535	

\* In this column ♀ indicates female, ♂, male

† The letters refer to the location in the heart from which the section was taken A from the septum wall near the base B from the posterior wall of the left ventricle near the base C, from the posterior wall near the apex, D, from the right ventricle near the base

TABLE 2—Summary of the Clinical and Postmortem Observations in the Dogs of Group 2

Dog	Sex	Weight, Kg.	Toxin per kg. Cc.	No Days Animal Lived After Injection of Toxin	Bile in Urine	Bile Pigment in Plasma	Urine	Icterymoses at Autopsy	Summary of Microscopic Observations				Icteric cardio-gram	L/R Ratio	L + R		Body Weight at Autopsy
									Heart	Lungs	Liver	Kidneys			Spleen	BW	
86	♀	7.00	0.00163	3	+	+	White cells +	0	Red cells scattered between muscle cells	Congestion, one necrotic area	Central necrosis, which is being replaced by regenerating liver cells	Areas in which tubular epithelium is flattened and tubules filled with cists small abscesses in cortex increase in interstitial tissue, glomeruli fibrotic and large	R <sub>2</sub> and R <sub>3</sub> decreased, then increased	1.39	0.00353	0.00732	
86	♀	9.77	0.00163	3	+	+		+	Granular appearance of muscle cells	Congestion	Central necrosis, congestion in necrotic areas, phagocytosis, round cell infiltration, cells resembling normoblasts	Infarct areas of necrosis of tubules, old scar on surface collections of round cells resembling normoblasts	R <sub>2</sub> and R <sub>3</sub> decreased	1.15	0.00532	0.00615	
87	♀	16.10	0.00163	3	+	+		+	Negative	Idem	Central necrosis phagocytosis, congestion necrotic area is collections of round cells resembling nucleated red cells	Small hemorrhagic areas	R <sub>2</sub> and R <sub>3</sub> decreased	1.07	0.00497	0.00395	
97	♀	16.20	0.00163	3	+	0	Red cells +, white cells +	+	Large bacilli	Congestion	Central necrosis, no traces of nuclei in the section, large bacilli	Fresh in fart	R <sub>2</sub> and R <sub>3</sub> decreased	1.26	0.00142	0.00168	

"9) ♂	11 00	0 00108	6	+	0	0	+	0	White cells +, occasional granular cysts	+	Negative	Conges- tion, edema	Central necrosis engorged with red cells, cells resembling nucleated red cells	Large area of necrosis including tubules and glomeruli, small areas of round cell infiltration, normoblasts	R <sub>2</sub> and R <sub>3</sub> decreased	1 26	0 00656	0 00715
102 ♂	11 00	0 00108	4	+	+	+	+	+	Trace of albumin epithelial cells and white cells in casts	+	Negative	Conges- tion	Central necrosis red cells in necrotic areas, cells resembling nucleated red cells	A few scat- tered necrotic tubules tubu- lary epithelium swollen epi- thelial cell nucleated casts	R <sub>2</sub> and R <sub>3</sub> decreased	1 12	0 00495	0 00563
103 ♂	11 20	0 00108	4	+	+	+	+	+	Marked trace of albumin, coarse granular casts	+	Negative	Pneu- monia	Central necrosis engorged with red cells, bile thrombi, cells resembling nucleated red cells	Necrosis of tubules, cysts	R <sub>2</sub> and R <sub>3</sub> decreased	1 19	0 00521	0 00576
104 ♂	11 02	0 00108	2½	0	0	0	0	0	Marked trace of albumin, occasional granular cyst	+	Area of hemor- rhage	Conges- tion hemor- rhage	Marked cen- tral necrosis, cells resem- bling nucle- ated red cells in collections of normal cells	Areas of round cell infiltration	R <sub>2</sub> and R <sub>3</sub> decreased	1 27	0 00084	0 00718
105 ♂	11 12	0 00108	7	+	+	+	+	+	Trace of albumin	+	Negative	Conges- tion, edema	Central necrosis, phagocyto- sis, collec- tion of round cells, cells resembling nucleated red cells	Interstitial changes glomeruli replaced by round, polymorpho nuclear and connective tissue cells	R <sub>2</sub> and R <sub>3</sub> decreased, then increased	1 31	0 00531	0 00616

\* In this column, ♀ indicates female, ♂, male

TABLE 3—Summary of the Clinical and Postmortem Observations in the Dogs in Group 2B

Dog	Sex*	Weight, kg.	Toxin per kg. Cc	Number Days Animal Lived After Injection of Toxin	Jaundice	Bile in Urine	Urine	Echymoses at Autopsy	Electro- cardiogram	L/R Ratio	L + R B W } Ratio	
											Initial Body Weight	Body Weight at Autopsy
107	♂	17.18	0.00135	12	0				No change	1.36	0.00165	0.00621
108	♂	19.15	0.00135	4	+	0	Faint trace of albumin	+	R <sub>1</sub> and R <sub>2</sub> decreased	1.37	0.00505	0.00535
109	♂	15.38	0.00135	16	0				R <sub>1</sub> and R <sub>2</sub> decreased, then increased	1.45	0.00193	0.00661
110	♂	13.85	0.00135	19	0				R <sub>1</sub> and R <sub>2</sub> decreased	1.30	0.00423	0.00622
111	♂	16.45	0.00135	11	0		Epithelial cells + white cells +	0	R <sub>1</sub> and R <sub>2</sub> decreased	1.23	0.00178	0.00662
112	♂	14.70	0.00135	13	0			0	No change	1.34	0.00500	0.00623

\* In this column, ♀ indicates female, ♂, male



TABLE 4—Summary of the Clinical and Postmortem Observations in the Dogs in Group 2 C

Dog	Sex	Weight, kg.	Toxin cc	Injection of Toxin	Days After Injection	Jaundice	Bile in Urine	Bile in Plasma	Urine	I echy- moses at Au- topsy	Microscopic Observations			Electro- cardiogram	L/R Ratio	L + R BW Ratio	
											Heart	Lungs	Liver	Kidneys		Initial Body Weight	Body Weight at Autopsy
88	♂	7.92	0.001	Fixed	0									No change			
89	♀	6.70	0.001	Fixed	0									No change			
91	♂	11.20	0.001	Fixed	0				White cells +++					No change			
101	♀	12.0	0.001	Lived	0	0	0	0	Few leu- kocytes, epithelial cells faint trace of albumin	0	Cells re- sembling fibro- blasts	Conges- tion, edema	Cont'd cells stain pale, but definite necrosis not present, phagocy- tosis, small areas of fibro- blastic tissue in central area, is though necrotic area had healed	Blood vessels engorged, bile stained casts	Heart block 3 days before death	0.00408	0.00792

\* In this column, ♀ indicates female, ♂, male

become ill, and did not show any clinical evidence of intoxication, except a loss of weight, which was as great as that in the dogs receiving the larger doses. These four dogs were still living and well twelve months after receiving the toxin. One dog (no 106) did not fall ill immediately after the injection, although ten days later it did, lost weight rapidly and died on the twenty-second day after the injection. At autopsy, jaundice and ecchymoses were not seen.

*Urine*—Examinations of the urine were made in the cases of several dogs. The specimens showed from faint to marked traces of albumin. Microscopically, a few leukocytes and epithelial cells were found following the injection of 0.001 cc of toxin (dog 101), and red cells, white cells and coarse granular and hyaline casts following the larger doses (as shown in tables 1 to 4).

The urines of ten dogs were tested for bile by Rosenbach's method (nos 85, 97, 99, 101, 102, 103, 104, 105, 106 and 108). Of these ten dogs four (nos 85, 102, 103 and 105 of tables 1 to 4) had bile in the urine, and the corresponding blood plasma of three showed the presence of bile pigments. In two dogs showing jaundice clinically (nos 97 and 99), neither the blood plasma nor the urine gave positive results in tests for bile.

*Effect on the Heart*—In the electrocardiograms of thirteen of nineteen dogs that had received each 0.00135 cc or more of toxin per kilogram of body weight there was a progressive decrease in the amplitude of waves  $R_1$  and  $R_2$  (dogs 81, 82, 84, 86, 87, 97, 99, 102, 103, 104, 108, 110 and 111 of tables 1 to 4). The electrocardiograms of dog 86 in addition to showing the decrease in  $R_1$  and  $R_2$  waves (fig 1 *A* and 1 *B*), also showed the development of  $S$  and  $S_1$  waves (fig 1 *C*). Changes were not apparent in the heart rate, the conduction time, the QRS interval and the T-wave. The records of dog 106 showed complete heart block for three days before death. This animal received only 0.001 cc of toxin per kilogram of body weight.

The L/R ratios of the hearts of the dogs into which diphtheria toxin had been injected, varied between 1.07 and 1.45 (tables 1 to 4). In all except dog 109, the ratio was less than the average L/R ratio of normal dogs (fig 2), that is to say, the left ventricle apparently lost more weight than did the right ventricle. But taken in conjunction with the ratio of the combined weights of the  $\frac{L+R}{B+W}$  ratios, the change in the ratio is probably to be ascribed to a loss of weight rather than to an actual right ventricular hypertrophy or a left ventricular atrophy in the short time of a few days.

The ratio of the combined ventricular weight ( $L+R$ ) to the body weight varied between 0.00468 and 0.00874 (as shown in tables 1 to 4). Twelve of the ratios were below the average for normal dogs and eight above the average (fig 3). If the weight of the animal just before the injection of diphtheria toxin was used in calculating the  $\frac{L+R}{B+W}$  ratio, this ratio in sixteen animals was below the average and in only four instances was above the average.

*Microscopic Examination*—Heart. In dog 83, microscopic sections were made from the septal wall of the heart near the base (*A*), from the posterior wall of the left ventricle near the base (*B*), from the posterior wall near the apex (*C*) and from the right ventricle near the base (*D*), as shown in table 1. In the other hearts, sections were taken from the posterior wall of the left ventricle. In none of these sections was there a striking change in the histologic appearance of the muscle fibers and the interstitial tissue. A section of one heart showed isolated red cells scattered between the muscle fibers, and sections of two other hearts showed the transverse striations not clearly marked.

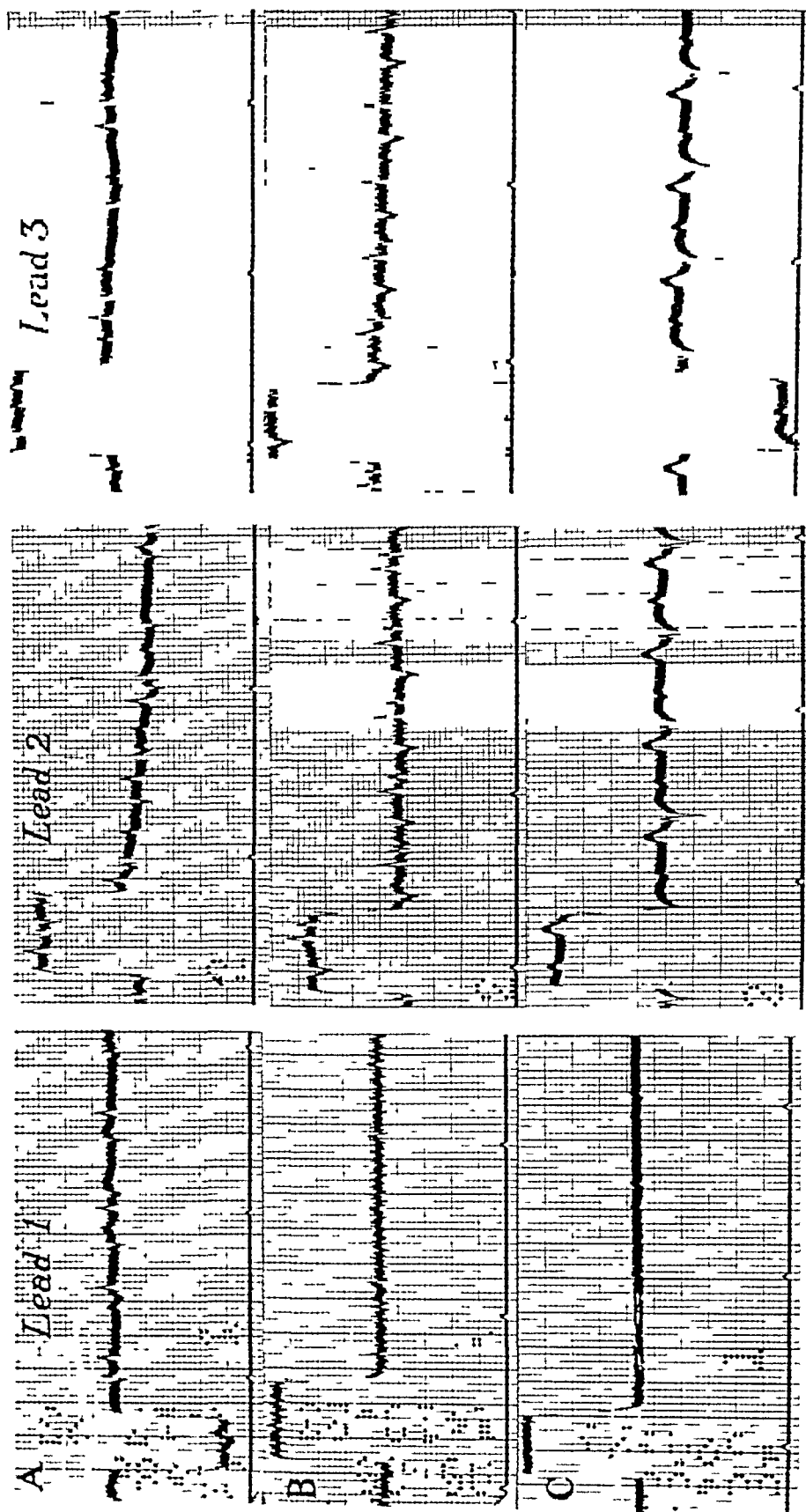


Fig 1—Electrocardiograms of dog 86 *A*, taken on Jan 17, 1923, before the injection of diphtheria toxin, *B*, taken on Jan 19, 1923, two days after the injection of 0.00168 cc of diphtheria toxin per kilogram of body weight, *C*, taken on Jan 20, 1923. Divisions of the ordinates equal  $10^{-4}$  volts. Divisions of the abscissae equal 0.04 second. Reduction, two-thirds natural size.

**Lungs** Sections from the lungs of several dogs showed fresh infarcts. Sections from others disclosed the capillaries engorged with red cells. Occasionally, large areas of leukocytic infiltration were seen, and in one section one of these areas had undergone necrosis. The alveoli were occasionally filled with edematous fluid staining a pale pink.

**Liver** The livers of these dogs showed more marked lesions than did any of the other organs. All the animals, except dog 106, showed necrosis of the central lobules to a greater or less extent usually marked. In a few cases, there was only

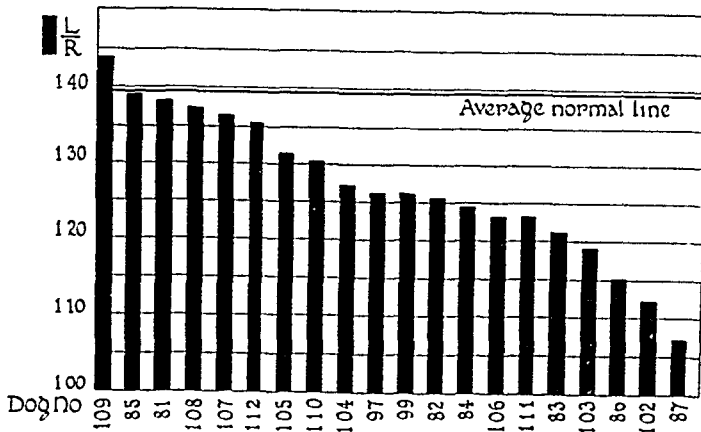


Fig 2—Showing the grouping of the L/R ratios, with reference to the average L/R ratio of normal dogs (average normal line). The heights of the solid columns represent the L/R ratios of the dogs that had received diphtheria toxin.

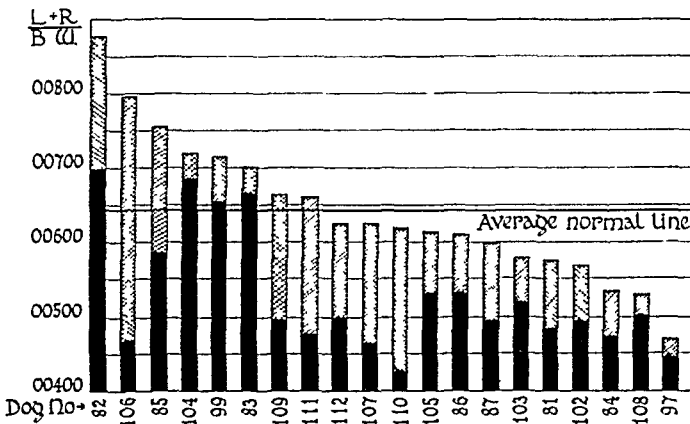


Fig 3—Showing the grouping of the  $\frac{L+R}{B W}$  ratios, with reference to the average normal line. The total height of a column represents the  $\frac{L+R}{B W}$  ratio when the weight of the dog at autopsy is used in the calculation of the ratio. The height of the solid column represents this ratio when the weight of the dog before the injection of diphtheria toxin is used in the calculation.

necrosis of a small area of cells in the center, while in others, the necrosis extended half way or more toward the periphery of the lobule. In some sections, there was a marked extravasation of red cells into the necrotic areas. The necrotic cells in many sections were undergoing phagocytosis by Kupffer cells, which contained brown pigment granules. Bile thrombi were occasionally seen. In all sections,

except those of dog 106, there were, in the centers of some lobules, collections of mononucleated cells of varying size and, in many, a few cells having the morphology of nucleated red cells. The nuclei were round and deeply stained, and the surrounding protoplasm was clear pink, or nearly the same tint as that of the red cells in the section. These cells suggested the presence of foci for the formation of new blood in the liver. I could not be certain, however, from examination of the sections that the cells were nucleated red cells. Unfortunately, blood smears were not examined for the presence of nucleated red cells in the circulating blood.

**Kidneys** Necrosis of the tubular epithelium was the most common renal lesion observed. The tubules toward the outer limits of the cortex seemed to be most frequently involved. In some sections there were large areas in which all the tubules were necrotic and nuclear elements were not seen, while in other sections, the necrosis was limited to scattered, isolated tubules. In sections from one animal, the tubular epithelium contained large vacuoles. Sometimes, the blood vessels were engorged with red cells, and occasionally there were fresh infarcts. In the sections from dogs 84, 86 and 99 collections of round cells were present in the interstitial tissue. The glomeruli in the kidneys of dogs 85 and 105 were in many places invaded by fibroblasts and round cells. In none of the sections was there a thickening of Bowman's capsule similar to that which Pritchett<sup>4</sup> observed in guinea-pigs following the injection of diphtheria toxin.

**Spleen** Sections were made from the spleens of four dogs. In two of these, pathologic changes were not observed. In the other two, there was marked engorgement with red cells.

**Summary**—Following the injection of diphtheria toxin intravenously, the dogs became ill, lost weight and frequently developed jaundice, death occurred from two and a half to twenty-two days after the injection. It was found that the injection of from 0.00135 to 0.00168 cc of toxin per kilogram of body weight was always followed within a few days by the symptoms described, but the animals receiving the smaller dose survived longer than those receiving the large one. A dosage of 0.001 cc per kilogram of body weight caused death in only one instance. In the animals receiving this dose the only symptom of intoxication was a loss of weight, which was as great as that in the dogs receiving the larger doses. Studies of the urine showed evidence of irritation of the kidneys, and examination of the urine and the blood plasma of dogs with jaundice showed, in several instances, the presence of bile. The electrocardiograms presented a progressive decrease in the  $R_2$  and  $R_3$  waves.

At autopsy, ecchymoses were frequently observed in the animals that had received the larger doses of toxin. The most striking of the microscopic observations was the central necrosis of the liver. The necrotic cells were frequently undergoing phagocytosis by Kupffer cells. In some sections there was marked extravasation of red cells into the necrotic areas. In most sections, in the centers of the lobules, collections of mononucleated cells of varying size were observed. Many of these cells had the morphology of nucleated red cells. The heart muscle was particularly lacking in any microscopic lesion that could be attributed to the toxin. The L/R ratios varied between 1.07 and 1.45, and the  $\frac{L+R}{B+W}$  ratios between 0.00468 and 0.00874.

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4 Pritchett, I. W. Pathological Effects of Diphtheria Toxin in the Guinea-Pig with Special Reference to a Lesion of Bowman's Capsule. *Am J Hyg* 2: 536, 1922.

## COMMENT

The pathologic changes that I observed at autopsy and microscopically in sections from dogs that had received injections of diphtheria toxin did not differ essentially from those reported by other investigators. I made observations, however, of the pathologic physiology that accompanied these changes. Jaundice following intoxication with diphtheria toxin is not frequently mentioned in the literature. It was observed by Courmont, Doyon and Pariot<sup>5</sup>. In my series it occurred in 66 per cent of the animals into which had been injected a dose of 0.00135 cc or more of toxin per kilogram of body weight. It seems most likely that the jaundice resulted from destruction of the blood by the diphtheria toxin (Stewart<sup>6</sup>). Courmont, Doyon and Pariot also described the central necrosis of the liver that I found in all the animals receiving 0.00135 cc or more of toxin per kilogram of body weight. Flexner<sup>7</sup> observed that the necrotic areas in the liver occurred more frequently in the center of the lobule than toward the periphery, while Du Bief and Bruhl<sup>8</sup> in a less extensive report, described scattered areas of necrosis, which were not limited to the central portion of the lobule.

*The Heart*—The frequency of sudden death in the course of clinical diphtheria has been the cause of much experimentation on animals in an attempt to discover the mechanism. The sudden death has been commonly supposed to be a direct result of heart failure. However, histologic examination of the heart muscle in patients who have died of diphtheria infection and in experimental animals that have received injections of diphtheria toxin has usually failed to reveal significant changes. MacCallum<sup>9</sup> from his experiments, concluded that death occurring at the height of an attack of diphtheria is not exclusively the result of a direct injury to the heart although this may play some part in the process. He suggested that a vasomotor paralysis may be involved. Marvin and Buckley<sup>10</sup> recently reported anatomic lesions in the ventricular and auricular musculature and in the conduction system

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5 Courmont, J., Doyon, M., and Pariot. Lesions hépatiques engendrées chez le chien par la toxine diphtérique, *Compt rend Soc de biol* **47** 610, 1895.

6 Stewart, H. J. A Study of Certain Effects Occasioned in Dogs by Diphtheria Toxin. II. An Analysis of the Mechanisms Possibly Responsible for the Alterations of the Heart, *Am J Path*, to be published.

7 Flexner, S. The Pathology of Toxalbumin Intoxication, *Johns Hopkins Hosp Rep* **6** 259, 1897.

8 Du Bief and Bruhl. Note sur une altération des cellules hépatiques dans la diphtérie expérimentale, *Compt rend Soc de biol* **43** 135, 1891.

9 MacCallum, W. G. The Mechanism of the Circulatory Failure in Diphtheria, *Am J M Sc* **147** 37, 1914.

10 Marvin, H. M., and Buckley, R. C. Complete Heart Block in Diphtheria, *Heart* **11** 309, 1924.

of the heart of a patient who had died of diphtheria. This patient had exhibited complete heart block before death. Numerous cardiac lesions in experimental animals have been described. Flexner<sup>7</sup> described degenerative changes in the muscle cells, including fatty degeneration, and lesions of the blood vessels. He did not find interstitial changes. Mollard and Regaud<sup>11</sup> described minutely changes in the morphology of the muscle cells, such as transverse and longitudinal fragmentation and nuclear degeneration, and changes in the blood vessels. Loth<sup>12</sup> described fatty infiltration and a "cooked appearance" of the muscle fibers in the hearts of guinea-pigs following the injection of diphtheria toxin. A study of my specimens did not reveal lesions of the heart muscle fibers or of the interstitial tissue that could be attributed to diphtheria toxin.

A decrease in the electrical potential as led off in leads 2 and 3 (fig 1) is observed in the decrease in the amplitude of waves  $R_2$  and  $R_3$  of the electrocardiograms. In all of my animals there was a decrease in the L/R ratio, which may have been reflected in the change observed in the electrocardiogram. The diphtheria toxin may indeed have injured the fibers so that their behavior, as recorded by the electrocardiogram differed from that of normal fibers. This difference was reflected in the decreased  $R_2$  and  $R_3$  waves. Nevertheless, I was not able definitely to interpret the changes.

In analysis of the data on the weights of the hearts, the figures of Herrmann for normal dogs were used. In his study, Herrmann sectioned the hearts of 200 normal dogs of various species and of about equal numbers of both sexes and calculated the L/R and  $\frac{L+R}{B+W}$  ratios. The normal L/R ratio, according to Herrmann,<sup>13</sup> is 1.393 and the normal  $\frac{L+R}{B+W}$  ratio is 0.00635. The L/R ratios of the hearts of the dogs in this series into which diphtheria toxin had been injected varied between 1.07 and 1.45. In all dogs, except dog 109, the L/R ratio was less than the average L/R ratio of normal dogs (fig 2). This would indicate that the left ventricle lost more weight than did the right ventricle. Taken in conjunction with the  $\frac{L+R}{B+W}$  ratios, the change in the

11 Mollard, J, and Regaud, C. Lesions experimentales du coeur provoques par la toxine diphterique, *Compt rend Soc de biol* **47** 828, 1895, Lesions chroniques experimentales du myocarde consecutives a l'intoxication diphterique, *ibid* **49** 674, 1897, Contribution a l'etude experimentale des myocardites. Lesions du myocarde dans l'intoxication aigue par la toxine diphterique, *Ann de l'Inst Pasteur* **11** 97, 1897.

12 Loth, M. The Heart in Diphtheria. A Clinical and Pathologic Study, *Arch Int Med* **31** 637 (May) 1923.

13 Herrmann, G. R. Experimental Heart Disease. I. Methods of Dividing Hearts, with Sectional and Proportional Weights and Ratios for Two Hundred Normal Dogs' Hearts. *Am Heart J* **1** 213 1925.

ratio is probably to be ascribed to the loss of weight which took place rather than to an actual right ventricular hypertrophy or a left ventricular atrophy in the short time of a few days. The marked decrease in the size of the x-ray shadow of the heart following the injection of 0.00135 cc or more of toxin per kilogram (Stewart<sup>6</sup>) is not inconsistent with such a view.

The ratio of the body weight (B W) to the combined ventricular weights (L + R) varied between 0.00468 and 0.00874 (as recorded in tables 1 to 4). Twelve of the ratios were below the average for normal dogs and eight above the average (fig. 3). If the weight of the animal just before the injection of the diphtheria toxin was used in calculating the  $\frac{L+R}{B\ W}$  ratio, this ratio was found below the average in sixteen animals and above the average in only four (tables 1 to 4). Since there was a considerable loss of weight by these animals and since it has been shown by Stewart<sup>6</sup> that loss of body weight does not influence the size of the heart, it was more accurate to use the initial figures in calculating the ratios.

#### CONCLUSIONS

Diphtheria toxin injected intravenously into dogs produces intoxication and death, if the dose is sufficiently large.

The injection of diphtheria toxin causes jaundice. If the cells in the liver (to which I called attention) are nucleated red cells, jaundice may have resulted from a destruction of red cells.

Central necrosis of the liver occurs when the dose of toxin is 0.00135 or more per kilogram of body weight.

Changes are not observable in the microscopic appearance of the heart muscle. Profound changes do, however, occur in the heart, as shown by the slight changes in the  $R_2$  and  $R_3$  waves of the electrocardiogram, the decrease in the  $\frac{L+R}{B\ W}$  ratio, the decrease in the L/R ratio and the decrease in the size of the heart.



# THE CAUSE OF DEATH FOLLOWING INTRAVENOUS INJECTION OF OX AND DOG SERUM INTO RABBITS<sup>\*</sup>

JACOB RABINOVITCH

ST LOUIS

Naunyn<sup>1</sup> observed that the intravenous injection of substances that have the power to destroy the erythrocytes of the animal into which the substances have been injected leads to the formation of intravascular fibrinous thrombi. Landois<sup>2</sup> was the first to attribute death following the intravenous injection of foreign serums chiefly to the occlusion of small pulmonary vessels by thrombi. He described the center of these thrombi as consisting of agglutinated erythrocytes around which fibrin was deposited. Ponfick,<sup>3</sup> on the other hand, denied the occurrence of thrombi following the injection of foreign serums. In this connection, it is of interest to refer to the work of Flexner,<sup>4</sup> who interpreted hyaline thrombi, found in certain infectious diseases and also produced experimentally by injections of substances that injure the erythrocytes, such as dog serum, ether and ricin, as consisting of agglutinated erythrocytes that subsequently have undergone secondary changes. After intravenous injections of lethal doses of dog serum or ether into rabbits, he found coagula filling the right side of the heart and the large pulmonary vessels. These coagula consisted of agglutinated red corpuscles, the formation of fibrin did not have any part in the origin of these thrombi. Pearce<sup>5</sup> also attributed the formation of thrombi and subsequent necrosis in the livers of dogs following the intravenous injection of serum of rabbits, which previously had been immunized with material obtained from the blood-containing organs or which had merely received injections of the bile of dogs, to the agglutination of erythrocytes caused by these serums.

Several years later, in continuation of his comparative studies on the coagulation of the blood and on thrombosis, Loeb,<sup>6</sup> with Strickler and Tuttle, analyzed the cause of death in rabbits after the intravenous

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1 Naunyn, B. *Arch f exper Path u Pharmacol* **1** 1, 1873

2 Landois. *Die Transfusion des Blutes*, Leipzig, 1875

3 Ponfick. *Virchows Arch f path Anat* **62** 273, 1875

4 Flexner, Simon. *J M Research* **8** 316, 1902

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6 Loeb, Leo, Strickler, A., and Tuttle, L. *Virchows Arch f path Anat*  
**201** 5, 1910

injection of dog serum or of ox serum. As did Landois, they found, after the injection of the foreign serums, occlusion of the pulmonary vessels by thrombi. However, they did not base their conclusions merely on the microscopic observations in the various organs of the animals into which the serums had been injected, but, in addition, made use of an experimental method that lent a much greater degree of certainty to their interpretation of the microscopic observations than a morphologic investigation alone could have done. By preventing the coagulation of the blood by the injection of solutions of hirudin, Loeb and his collaborators were able to show that, after the injection of dog serum, the rabbit succumbed to the occlusion of the pulmonary vessels by fibrinous thrombi, for hirudin, by inhibiting the development of these thrombi, prolonged the life of the rabbits, and, in a number of cases, prevented death. On the other hand, hirudin was ineffective after the injection of ox serum because the latter substance does not cause the formation of fibrinous thrombi, but of thrombi consisting of agglutinated erythrocytes. These results corresponded with those of experiments *in vitro* in which the action of dog serum and ox serum on rabbit blood was correlated with the symptoms following the injection and also with the microscopic appearances in the organs of the animals that had received the injections. The thrombi following the injection of dog serum were the type of thrombi due to the formation of fibrin, and those following the injection of ox serum were the type caused by agglutination of red cells.

Soon afterward, Zinsser<sup>7</sup> studied the cause of death following the intravenous injection of goat serum in rabbits, he excluded hemagglutinations as the cause of death, but admitted the possibility that hemolysis was a factor. However, Zinsser did not make use of an anticoagulation substance, nor did he report microscopic observations in the lungs of the animals into which injections had been made. Recently, Aronson<sup>8</sup> concluded that the hemagglutination and the hemolytic and necrotizing actions of goat serum are due to one and the same substance.

Kusama,<sup>9</sup> repeating the experiments of Loeb and his collaborators, could not confirm the prolongation of life which the latter investigator had observed when the injections of dog serum were combined with injections of hirudin. Kusama attributed the death following injection of the foreign serum to the increased viscosity of the blood leading to stasis in various organs—without, however, giving any proof of this condition. This author, furthermore, asserted that the increased coagulability of the blood of the rabbit following the injection of dog

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7 Zinsser, Hans. *J. Exper. Med.* **14** 25, 1911.

8 Aronson, J. D. *J. Immunol.* **15** 465, 1928.

9 Kusama, S. *Beitr. z. path. Anat. u. z. allg. Path.* **5** 55, 1913.

serum was due to disintegration of the blood platelets, and he denied the existence of fibrinous thrombi in this case, as reported by Loeb

Still another view concerning the death of rabbits following the intravenous injection of foreign serums was expressed by Coca,<sup>10</sup> who interpreted it as due to a constriction of the pulmonary vessels following the intravenous injection of the serum. Coca's view was based on the fact established by Airila,<sup>11</sup> Coca and Drinker and Bronfenbrenner<sup>12</sup> that, in animals made anaphylactic through sensitizing injections of a foreign serum, subsequent injections cause a constriction of the pulmonary vessels that leads to the death of the animal. Coca, however, did not carry out experiments in animals not previously sensitized to foreign serums. More recently, Friedberger and Seidenberg<sup>13</sup> showed that perfusion of the isolated lungs of animals with foreign serums actually leads to a constriction of the pulmonary vessels.

Thus, three views may be distinguished concerning the cause of death following the intravenous injection of foreign serums in rabbits: (1) the view expressed by Loeb, Strickler and Tuttle that death is due to the occlusion of the pulmonary vessels by thrombi following the intravenous injection of hemolytic serums and to the occlusion by agglutination of erythrocytes following the injection of agglutinative serums, (2) the view of Kusama that death is due to increased viscosity of the blood, and (3) the view of Coca that death is due to constriction of the vessels independent of thrombi.

Because of these marked divergencies of opinion concerning the mode of action of foreign serums in causing death after intravenous injection, I repeated and extended in various directions the investigations of Loeb and his collaborators and of Kusama.

#### EXPERIMENTS WITH OX SERUM

*Preparation of Ox Serum for Injection into Rabbits*—The blood was obtained in the slaughter house and was collected in a sterile vessel, the first blood flowing out of the wound was discarded. The blood was allowed to clot and was then kept in the refrigerator for twenty-four hours, during which the clot retracted and the serum separated. The serum thus obtained had, as a rule, a reddish tinge, but became clear after centrifugation. It was found that when the serum was kept continuously in the refrigerator, it remained active for a number of days. Fresh blood, however, was obtained twice weekly so that not at any time was the serum used in my experiments more than four days old. Before injection, the serum was warmed to body temperature, it was then injected under aseptic conditions into the ear vein of a rabbit at a slow rate, usually that of from 3 to 4 cc per minute.

<sup>10</sup> Coca, Arthur. *J Immunol* **4** 219, 1919.

<sup>11</sup> Airila, Y. *Skandin Arch f Physiol* **31** 388, 1914.

<sup>12</sup> Drinker, C. K., and Bronfenbrenner, Jacques. *J Immunol* **9** 387, 1924.

<sup>13</sup> Friedberger, E., and Seidenberg, S. *Ztschr f Immunitätsforsch u exper Therap* **51** 276, 1927.

1 *Injection of Lethal Doses of Ox Serum*—In the large majority of cases, the dose of serum that killed a rabbit within from three to five minutes after its injection ranged from 7 to 8 cc per kilogram of the weight of the animal. There were, however, occasional variations, depending on the kind of rabbits used, some being more susceptible to the serum than others, e.g., it was found that, in general, gray rabbits were less susceptible than white rabbits.

When a lethal dose of ox serum was injected, the animal became dyspneic almost immediately after completion of the injection, or, at times, even in the course of the injection. This condition was soon followed by gasping for air, a shriek, opisthotonus, convulsions and death.

At autopsy, which was performed immediately after death, I found all the chambers of the heart still beating, at times rhythmically and at other times arrhythmically. The right side of the heart was usually markedly dilated, but gross coagula could not be found in the heart or the larger vessels. The lungs were a normal pink, but showed occasional edema, and possibly areas of a telecystasis. The occurrence of edema seemed to depend on the length of time elapsing between the injection and death, in those animals in which death was rapid, i.e., within from three to five minutes after the injection of the serum, edema of the lungs could not, generally, be found. In those cases in which death was delayed to from ten to fifteen minutes after the injection, or longer, edema of the lungs was observed frequently. None of the other organs examined, spleen, liver, kidney, brain, etc., showed any gross pathologic lesions.

The microscopic examination of the various organs revealed serious lesions only in the lungs. There was marked dilatation of the lung capillaries, and these were occluded by hyaline thrombi, which seemed to be composed of agglutinated red corpuscles. Definite outlines of the individual red cells could not be made out in the capillaries. I found only occasional clumps of blood platelets in some of the capillaries. These did not, therefore, seem to play an important role in the formation of the thrombi. The larger vessels, particularly the pulmonary veins, were filled with red cells, white cells and some elements that might have been blood platelets. These platelet-like structures, however, lacked definite outlines. I found, also, in the larger veins, disintegrated blood cells that were not unlike blood platelets. A striking feature was the entire absence of any visible fibrin in the capillaries or in the larger blood vessels. This absence of fibrin suggested that the occlusion of the blood vessels by the hyaline thrombi was not due to a process of coagulation, but essentially to an agglutination of the red cells. All the other organs examined microscopically showed merely congestion. The brain failed to present any pathologic lesion that might have accounted for any of the symptoms observed, or for the death of the animal following the injection of the ox serum.

In view of such a widespread occlusion of the pulmonary capillaries, following the injection of a lethal dose of ox serum, it is reasonable to assume that a state of asphyxia developed, owing to the difficulty which the blood had in moving from the right to the left ventricle of the heart. In addition, the diminution in the volume of the alveolar spaces of the lungs, as a result of the great distention of the capillaries, may have intensified the asphyxia. These conditions gave rise to all the symptoms and finally caused the death of these animals. These effects were perhaps still further intensified by the marked stagnation of the blood in all the other organs, especially in the heart, liver, kidneys and spleen.

*Injection of Sublethal Doses of Ox Serum*—When, instead of from 7 to 8 cc of ox serum per kilogram of the weight of the animal, I injected a sublethal

dose, namely, from 4 to 5 cc per kilogram of weight, the rabbits appeared perfectly well and seemed unaffected by the injection. When these animals were killed within from ten minutes to twenty-four hours after the injection of the serum, I found in the organs that appeared normal to the eye certain microscopic changes much like those I have just described as occurring in rabbits dying after receiving a lethal dose, namely, scattered areas in which the capillaries in the lungs were occluded by hyaline thrombi. However, there existed an important difference between these two groups of animals. Whereas, in the group that had received the injection of lethal doses of ox serum, practically all the capillaries were occluded, in the group that had received the injection of sublethal doses, only a small number of capillaries were affected. This difference in the degree of occlusion of the capillaries in these cases explains the difference between the results obtained with lethal and those obtained with sublethal doses of serum. In the former instance, the more complete occlusion of the capillaries led to the death of the animals, whereas, in the latter instance, the circulation and aeration of the blood were not sufficiently interfered with to call forth any serious symptoms.

These results lead, therefore, to the conclusion that the changes in the vessels of the lungs are responsible for the asphyxia observed after the injection of ox serum, also that the changes noted in other organs are only secondary to the interference with the pulmonary circulation and are, at best, of secondary significance.

*Effect of Heparin in the Formation of Thrombi in Rabbits Following Injection of Ox Serum*—In order to find corroborative evidence of the absence of fibrin in the thrombi that form in the capillaries of the lungs after the injection of ox serum, I sought to determine how far intravenous injection of heparin, either preceding the injection or in combination with the latter, influences the results of the administration of this serum. In this connection, it may be recalled that, in his earlier experiments, Loeb had used hirudin for similar purposes and found it ineffective. I injected from 5 to 10 mg of heparin per kilogram of the weight of the animal, a quantity sufficient to prevent the coagulation of the blood in the rabbit thus treated. I found that the addition of this substance did not prolong the life or prevent the death of the animal after the administration of an ordinarily lethal dose of ox serum. Furthermore, both the macroscopic and the microscopic pictures of all the organs from the animals treated with ox serum plus heparin were exactly the same as those of the organs from animals into which ox serum alone had been injected.

One may therefore conclude that the formation of the thrombi in the capillaries of the lungs following the injection of sufficient amounts of ox serum is a result of an agglutination of the red cells, and does not depend on the formation of fibrin, enveloping and binding together the red cells into a thrombus. If the thrombi that develop after the injection of ox serum were the result of the formation of fibrin, one should expect heparin, which, in the amount injected, has a pronounced anticoagulating effect, at least to retard or, perhaps, prevent altogether the occurrence of the thrombi and the death of the animal.

*Changes in the Blood Cell Count in Rabbits into Which Ox Serum Had Been Injected*—Inasmuch as I had assumed that the injection of ox serum leads to a retention of cellular elements of the blood in the lungs and in other organs, but that this does not lead to hemolysis, it was of interest to follow the fate of the blood cells by means of counts of the various elements of the blood, made at different times after the injection of the serum

In the normal rabbit, the blood counts were as follows: red blood cells from 5,000,000 to 6,000,000, white cells, from 8,000 to 9,000, and blood platelets from 500,000 to 600,000 per cubic millimeter. The platelet count was made according to the method of Reimann<sup>14</sup>. From three to five minutes after the injection of a lethal dose of the ox serum, a definite decrease was noted in all the cellular elements of the blood, the number of the red cells was then from 2,000,000 to 3,000,000, that of the white cells, from 3,000 to 4,000, and that of the blood platelets from 100,000 to 200,000 per cubic millimeter. These animals usually died within from six to seven minutes after the injection of serum.

When a sublethal dose of ox serum (from 5 to 6 cc per kilogram of the weight of the rabbit) was injected, during the first two minutes following the injection, no marked change was found in the cellular elements of the blood, but after from three to five minutes there occurred a marked reduction in the counts of all the cells. Thus, the red cells were found numbering only from 2,000,000 to 3,000,000, the white cells from 4,000 to 5,000 and the platelets about 150,000 per cubic millimeter. These numbers then diminished continuously until two hours after the administration of the serum, when the minimal count was reached. At this period, the count of the red cells decreased sometimes to less than 1,000,000, while the count of the white cells fell to 2,000 or 3,000 and that of the platelets to 50,000 or 60,000 per cubic millimeter. In other cases, however, the decline in the cell counts after two hours was less pronounced, the red cells numbering about 3,000,000, the white cells 6,000, and the platelets 300,000 per cubic millimeter.

But this great reduction in the cellular elements of the blood was only temporary, counts made twenty-four hours after the injection of serum showed a general tendency of the numbers of blood cells to return again to higher figures. I found, for instance, the number of red cells at that time to be about 4,000,000, of white cells 4,000 and of platelets about 400,000, though the number of all the cellular elements of the blood, while it was increased, was still distinctly lower than normal.

The increase that I found after twenty-four hours must have been largely due to the freeing of the cells that had been retained in the capillaries of the various organs. It is not probable that the red cells that had been agglutinated could secondarily separate from each other. However, the masses of stagnating blood corpuscles that I found shortly after the injection of sublethal doses of ox serum had greatly diminished after twenty-four hours.

These results are interesting in view of the fact that they agree with our conclusion that the cellular elements of the blood are retained in the capillaries, especially in the lungs, but also in other organs, and this retention concerns the red cells, as well as the leukocytes and the platelets.

*Immunization of Rabbits Against Ox Serum*—In his experiments, Loeb succeeded in producing in rabbits a marked immunity to the lethal effects of

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14 Reimann, H. A. J. Exper. Med. 40 553, 1924

dog serum, on the other hand, in preliminary experiments, he found it impossible to produce a similarly pronounced immunity to ox serum. I made some experiments in which I determined whether, through repeated intravenous injections of sublethal doses of ox serum, it was possible to achieve a diminution in the severity of the symptoms following the injection of a lethal dose, and to delay or prevent the death following such an injection.

Five rabbits were used for this purpose, all of which received every second day intravenous injections of ox serum, 4 cc being injected at the start and then gradually increasing amounts, 5 cc, 6 cc, 7 cc and 8 cc per kilogram of the weight of the animal. Of the animals thus immunized which had received injections of a minimal lethal dose of the serum one week following the last immunizing injection, three died about fifteen hours after the injection, while two were still alive twenty-four hours afterward. At this time, the animals were killed and their organs removed for examination.

Sections of the lungs from the immunized rabbits, the life of which had been prolonged, but which died about fifteen hours after the injection of the serum, showed, as a rule, marked edema of the lungs and occlusion of the vessels by agglutinated red cells. This picture was similar to that observed in the nonimmunized rabbits. I also found, in these cases, occlusion of the pulmonary vessels by a material that was either blood platelets or disintegrated red cells. On the other hand, in sections of lungs taken from rabbits that were still alive after twenty-four hours, I found occlusion of the capillaries by agglutinated cells only in certain parts of the lung. The occlusion was therefore less marked in these animals, and edema of the lungs was entirely lacking.

#### EXPERIMENTS WITH DOG SERUM

*Injections of Dog Serum*—In these experiments, the blood was obtained from the jugular vein of a dog, and the serum was separated from it in the manner described in the case of ox serum. The lethal dose of the dog serum was found to be similar to that of the ox serum, namely, from 7 to 8 cc per kilogram of the weight of the animal. Likewise, the symptoms resulting from the injection of a lethal dose were the same: dyspnea, gasping for air, shrieking, opisthotonus, convulsions and death. At autopsy, performed immediately after the death of the animal, I found the right side of the heart much dilated and the heart chambers of both the left and the right side still beating, sometimes rhythmically and at other times arrhythmically. If death occurred within the first ten minutes after the injection of serum, gross coagula were found in the right side of the heart, extending into the vena cava and the portal vein, as well as into the pulmonary veins. In cases in which death was delayed for longer than ten minutes, clots were not seen in the heart or the larger veins. The lungs did not show, as a rule, any gross pathologic lesion, with the exception of occasional edema, the latter condition depending on the length of the period elapsing between the injection of serum and the death of the animal, the longer this period, the more frequent and extensive was the edema in the lungs. All the other organs examined, spleen, liver, kidneys, brain, etc., appeared normal to the naked eye.

Microscopic examination of the various organs showed the main lesion to be in the lungs, as in the case of the injection of ox serum. The pulmonary changes consisted in widespread dilatation of the capillaries and occlusion by red cells massed-together. While it was difficult to recognize fibrin in the capillaries, in the larger veins deposits of fibrin could readily be seen. A marked hemolysis

of the red cells was also noted, this condition is of interest, especially because it is probably responsible for the formation of fibrin within the vessels

One may assume, therefore, that the occlusion of the capillaries by thrombi is the cause of death after the injection of dog serum as well as after the injection of ox serum. However, the cause of the formation of the thrombi is not the same in both cases. After the injection of ox serum, one has to deal with thrombi due to agglutination, whereas following the injection of dog serum, the finding of fibrin clots in the larger veins indicates a process of coagulation leading to the formation of fibrinous thrombi.

*Effect of Heparin on Rabbits Following Injection of Dog Serum*—In order to test this conclusion, I carried out experiments in which heparin was injected intravenously into rabbits simultaneously with or preceding the injection of dog serum. In these experiments, from 5 to 10 mg of heparin per kilogram of the weight of the animal was injected. It was then found that, whereas the animals that had not received injections of heparin died within from five to ten minutes after the injection of a lethal dose of dog serum, the rabbits receiving a suitable amount of heparin in addition to the serum lived for a much longer period and in some cases, seemed to be unaffected by the serum up to the moment that they were killed, almost twenty-four hours after the injection. In order to obtain these results, it was necessary to guard against the use of too large a quantity of heparin, in two cases in which 20 mg of heparin per kilogram of weight was injected, the animals died within fifteen minutes. But, even in these cases, the controls died in a shorter time, namely in from five to ten minutes after the administration of the dog serum. When an excess of heparin was injected, there seemed to be a marked tendency to extensive hemorrhages, especially in the lungs, but also in the liver, spleen and kidney, and it is probably this condition that hastens the death of the animals in such cases. On the other hand, when too small a quantity of heparin was injected, the process of coagulation was not prevented, and there was, therefore, only a temporary delay in the death of the animals, usually extending over several hours.

It was also interesting to note that the microscopic examination of lungs of rabbits that lived for twenty-four hours following combined injections of serum and heparin and were then killed, did not show any noticeable deviation from the normal, there was no evidence of the formation of thrombi in the capillaries or the larger vessels.

When in combination with heparin, a dose of dog serum was injected which, in a rabbit not receiving heparin would have been lethal within from five to ten minutes, but which, under these circumstances, was not lethal, and when this animal was killed at the time when the control animal died, I found in the lungs of the former a complete absence of thrombi, in contrast with what I found in the lungs of the latter the capillaries and the vessels, as usual, occluded by thrombi.

All these experiments make it evident that the occlusion of the capillaries in the lungs of the animals receiving injections of dog serum is due to the formation of fibrinous thrombi, in which the cellular elements of the blood, especially the red cells, are enmeshed. These masses of



red cells are much paler than the agglutinated erythrocytes that occlude the vessels in the lungs of the rabbits receiving injections of ox serum. This difference is due to the hemolytic action that dog serum exerts on rabbit corpuscles in contradistinction to the action of ox serum, which is essentially agglutinative in its effects. Thus, the thrombi found after the injection of dog serum have the appearance of pale, hyaline, homogeneous masses, the thrombi following the injection of ox serum, which allows a much better preservation of the individual blood cells, show clearly outlined erythrocytes. These results confirm the previous observations of Loeb, who used hirudin instead of heparin. They contradict the negative observations subsequently published by Kusama. The latter's erroneous conclusions are probably to be charged to the fact that he used unsuitable concentrations of the anticoagulant.

*Changes in the Blood Cell Counts in Rabbits into Which Dog Serum Had Been Injected*—When lethal doses of dog serum were injected intravenously into rabbits, there resulted a pronounced diminution in all the cellular elements of the blood. Thus, in my experiments, within five minutes after the injection

TABLE 1—*Effect of an Injection of a Sublethal Dose of Dog Serum on the Blood Cells in Rabbits*

Time of Count	Red Cells	White Cells	Blood Platelets
Before injection of serum	5,000,000	9,000	510,000
5 minutes after injection	3,180,000	8,600	460,000
30 minutes later	3,600,000	10,400	
2 hours later	3,450,000	7,000	
24 hours later	3,780,000	17,400	485,000

of the serum the red cells were found to have decreased from an original number of 5,000,000 to 1,500,000, the white cells from 9,000 to 2,000 and the platelets from 500,000 to 150,000. On the other hand, when sublethal doses of dog serum were injected (from 4 to 5 cc of the serum per kilogram of the weight of the animal) only the erythrocytes showed any significant diminution. Five minutes after the injection, the white cells and the platelets being only slightly affected. Twenty-four hours later, the number of red cells still remained at the same reduced level, whereas the number of white cells showed, as a rule, a considerable increase over the original number. The number of the platelets remained about normal. The results of the counts are given in table 1.

The results set forth in table 1 as following the injection of a sublethal dose of dog serum are strikingly different from those observed after the injection of a sublethal dose of ox serum, in the latter case, a tendency was shown for all the cellular elements in the blood to return to normal after a period of twenty-four hours.

When heparin was injected in suitable amounts together with an ordinarily lethal dose of dog serum, the animal survived and the blood cells did not show any abnormal quantitative change. The results of the counts are given in table 2.

The question arises as to the manner in which heparin prevents the diminution in the cellular elements of the blood. It may do this indi-

irectly by preventing the foimation of fibrinous thrombi in which a certain number of blood cells are caught Another possibility is that heparin may prevent hemolysis In order to determine whether heparin has any effect on hemolysis, I carried out experiments in vitro

I first ascertained the minimal quantity of dog serum required to hemolyse, within one minute, 1 cc of a 5 per cent suspension of rabbit's erythrocytes in 0.9 sodium chloride solution and found it to be 0.8 cc I then noted that 0.5 cc of a 5 per cent solution of heparin delayed hemolysis of the mixture of serum and red cells for at least two hours, whereas 3 cc of the solution of heparin prevented hemolysis altogether

These experiments showed that heparin is capable of preventing the hemolysing action of dog serum on rabbit blood The mechanism, therefore, through which heparin, when used in vivo together with dog serum, hinders the reduction in the number of cellular elements of the blood, is probably two-fold, it acts by preventing the formation of fibrinous thrombi and, thus, the retention of the blood cells, and also

TABLE 2—*Effect of an Injection of a Mixture of Heparin and a Lethal Dose of Dog Serum on the Blood Cells in Rabbits*

Time of Count	Red Cells	White Cells	Blood Platelets
Before injection of serum	6,930,000	14,600	520,000
5 minutes after injection	6,390,000	15,800	500,000
1 hour later	6,030,000	15,600	
2 hours later	6,320,000	9,000	
24 hours later	6,510,000	12,000	495,000

by inhibiting hemolysis It therefore prevents the formation of fibrinous thrombi in a double manner (1) by preventing coagulation of the blood and (2) by exerting a certain protective influence on the erythrocytes so that thrombokinase or tissue coagulin, which induces the process of coagulation, is not set free

If, now, the effects of dog serum and ox serum on the blood cells of the rabbit are compared, it is found that, when either of these serums is injected in lethal doses, a pronounced reduction of all the cellular elements of the blood results, but that, when these serums are injected in sublethal doses, there is a difference in their effects Ox serum produces a temporary reduction of all the cells in the blood, which, in the course of twenty-four hours, gives place to a return to normal Dog serum, on the other hand, produces a noticeable reduction only of the erythrocytes, the white cells and the platelets being little affected within the first few hours after the injection of the serum, there is no tendency on the part of the erythrocytes, after the lapse of twenty-four hours, to reach normal counts again, the white cells, on the other hand, surpass now their original number, and the number of the platelets remains practically unchanged Furthermore heparin does not

affect the action of ox serum on blood cells in rabbits, but when it is mixed with dog serum, it prevents the reduction in number of the blood cells. As has been seen, ox serum causes a diminution of the number of the blood cells through the formation of thrombi by a process of agglutination and through retention of the cells in various organs, dog serum, on the other hand, produces corresponding effects by the formation of fibrinous thrombi and by hemolysis. In the case of the injection of ox serum, blood cells which are loosely agglutinated or held back in various organs are, after some time, carried back into the general circulation, but, in the case of the injection of dog serum a considerable number of erythrocytes have been destroyed through hemolysis, while other cellular elements are firmly retained in the fibrinous thrombi and cannot be restored to the circulation. It is only through prevention of hemolysis and prevention or lessening of the formation of fibrinous thrombi that this loss in the number of blood cells can be forestalled after the injection of dog serum.

While it thus seemed certain from our sets of experiments that the cause of death in rabbits receiving a lethal dose of dog serum is occlusion of the capillaries and larger vessels of the lungs by fibrinous thrombi, there still remained the possibility in the case of ox serum that constriction of the pulmonary vessels might, after all, be the real cause of death, and that the presence of thrombi composed of agglutinated red cells was merely simulated. I attempted, therefore, to determine directly the occlusion of the pulmonary vessels by examining on glass slides thin slices of lung that had been rapidly removed from the rabbits before secondary changes could take place, following the injection of lethal doses of ox serum. By exerting gentle pressure on the lung tissue, I could squeeze out from the vessels numerous thrombi consisting of agglutinated red cells, which were readily seen under the microscope. When the same experiment was carried out with pieces of normal lungs, thrombi consisting of agglutinated erythrocytes could not be squeezed out from the vessels. These results demonstrated, therefore that thrombi consisting of agglutinated erythrocytes actually do occlude the pulmonary vessels. The results thus corroborated my previous observations according to which the thrombi formed in the capillaries of the lungs by agglutination of erythrocytes are primarily responsible for the death of the animal receiving a lethal dose of ox serum. There remains, of course, in addition to the formation of thrombi, the possibility that, in the case of agglutinative serums, a constriction of the pulmonary vessels may play a certain rôle, but, at best, it could only be a subsidiary one. The microscopic examination of the lungs of rabbits following the injection of ox serum does not show any changes suggesting a constriction of vessels in the lung.

## COMMENT

My investigations confirmed the conclusions of Loeb that death in rabbits following the intravenous injection of dog serum and ox serum is, in the main, due to the occlusion of the pulmonary vessels by thrombi, which, in the case of ox serum, are caused by a process of agglutination, and, in the case of dog serum, by the formation of fibrin. In order to distinguish between these two types of thrombi, it was necessary to use microscopic in addition to biochemical methods, and employ anti-coagulative substances, such as hirudin and heparin, which prevent the formation of fibrinous thrombi. If, by means of these substances, it is possible to prevent the death or, at least, prolong the life of the rabbits following the injection of the hemolytic serums, one may conclude that the fibrinous thrombi that occluded the vessels of the lung were the actual cause of death in the animals.

My investigations did not confirm the experimental results and conclusions of Kusama. In particular, I showed that contrary to his observations, heparin, acting in a manner similar to that of hirudin, does delay or prevent the death of rabbits that otherwise would quickly have followed the intravenous injection of dog serum. The changes that I described as occurring in the number of the blood cells under various conditions after the injection of foreign serums, the effect of immunization of rabbits against ox serum and, further, the correlation between microscopic alterations in the lung and the symptoms following the injection of ox serum, all agree with these views.

My conclusions as to the relation between death and the type of thrombi that occlude the blood vessels after the injection of ox serum and of dog serum are, thus, in the first place, based on the perfect correspondence that was found to exist between the amounts of serum injected and the general effects of the injection on the condition of the rabbit, and between the graded gross and microscopic changes that were observed under these conditions in the pulmonary vessels. In the second place, they are based on the differences in the effects of heparin when administered in combination with dog serum and ox serum.

From these two sets of data, I conclude that it is mainly the erythrocytes, either with or without the formation of fibrin, that occlude the capillaries, after the injection of the foreign serums, and that blood platelets, if they play any part at all, are only of minor importance in this process. In the case of dog serum, the erythrocytes occlude the vessels because they are retained there by fibrin, which is set free as the result of the destruction of the erythrocytes, whereas, in the case of ox serum, the erythrocytes are held back in the vessels because they agglutinate with each other.

While, in the case of ox serum, which has essentially agglutinative effects, the use of heparin, in accordance with expectations, did not

prevent the death of the animal, I showed that here thrombi due to agglutination actually did occlude the pulmonary vessels. However, I could not definitely exclude the possibility that a constriction of the vessels may not be an additional factor in the death of the animal following injection of ox serum, although I did not find any fact making for such a conclusion.

#### SUMMARY

Death in rabbits following intravenous injections of either ox serum or dog serum is due primarily to massive occlusion of the lung capillaries by thrombi, and secondarily, perhaps, to the stagnation of blood in other internal organs. There is a possibility that, in the case of ox serum, constriction of blood vessels may be an additional factor, although I did not find any definite indication that this is the case.

Injections of ox serum produce thrombi in the lung capillaries by a process of agglutination, whereas injections of dog serum produce them by causing the formation of fibrin. In agreement with this conclusion is the fact that heparin does not have any effect in preventing the formation of thrombi in the case of injections of ox serum, but is effective when used in combination with dog serum, also that heparin does not prolong the rabbit's life when used in combination with ox serum.

The injection of a lethal dose of either ox serum or dog serum results in a pronounced diminution in the numbers of all the cellular elements of the blood in the peripheral circulation. The injection of sublethal doses of serum, however, in the case of ox serum, brings about a reduction in the number of blood cells only temporarily. In the case of dog serum, the reduction is more permanent. The differences in the quantitative changes in the cellular elements of the blood following the use of these two serums, as well as the differences in the action of heparin on these changes, are in accordance with the difference in character of the thrombi formed after the injection of the two serums. In addition, I found that heparin exerts a certain inhibitory effect on the hemolysis of rabbit's erythrocytes which normally takes place under the influence of dog serum.

# THE COARSER HISTOLOGIC VARIATIONS OF THE THYROID GLAND\*

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That the microscopic appearances of supposedly normal thyroid glands are subject to considerable variation is well known, but whether the variations of its various appearances can be systematized and correlated with the ages, the physiologic conditions or the morbid states of the patients from whom the glands are taken, does not seem to have been adequately investigated

It was therefore decided to make a preliminary survey of the subject by a careful study of such variations as might be discovered in 100 glands that did not present any signs of local disease, and had been taken from patients of various ages who died of many different diseases

## MATERIAL

Most of the material was obtained at necropsies performed in the Philadelphia General Hospital, where the greater number of the patients are of advanced age and die of chronic diseases. The age, sex and color of the patients from whom the material was collected are set forth in table 1. The diseases causing death in the patients are shown in table 2.

As scarcely any death from disease can be referred to a single factor, and as the greater the age the more numerous the contributing factors are apt to become, it was impossible to reduce this tabulation to desirable simplicity. For example, some patients with cardiovascular disease had syphilis, the patient dying suddenly of a ruptured aneurysm, of course, had syphilis and vascular disease. When, in such cases, a distinctive appearance of the thyroid was discovered the question arose: To which of the associated conditions was it to be attributed? In the investigations to be considered, we attempted to overcome this difficulty by making many subordinate groups—one, indeed, for every morbid condition mentioned in the necropsy protocols as having been found in the body from which the tissue was derived—and examining each group separately to see whether or not the microscopic variation seemed to occur frequently in it.

Thus a gland from a patient, aged 70, with advanced cardiovascular disease and cancer of the breast, who died of bronchopneumonia, was tabulated in the appropriate age group with all the other glands taken from persons of the same age group, in the cardiovascular group with all the other glands from persons with cardiovascular disease, irrespective of age, other disease or cause of death, in the carcinoma group with all the other glands taken from persons with carcinoma,

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irrespective of associated and complicating diseases, and in the bronchopneumonia group with all the other glands taken from persons with bronchopneumonia, irrespective of other factors that might have been contributory to the terminal condition

The thyroid tissues, as they were collected, were placed in neutral formaldehyde for fixation, and subsequently embedded in celloidin for cutting, because experience

TABLE 1—*Sources of the One Hundred Thyroid Glands Examined in This Study*

Life Decade	Male	Female	White	Black	Total
1	2	2	3	1	4
2	1	1	1	1	2
3	8	6	6	8	14
4	9	2	3	8	11
5	16	8	12	12	24
6	11	6	13	4	17
7	13	6	12	7	19
8	12	5	13	4	17
9	0	1	1	0	1
Total	72	37	64	15	109

TABLE 2—*Diseases Causing Death in the Patients Whose Thyroid Glands Were Examined*

	Disease	Male	Female	White	Black
1	Acute Cases Noninfectious				
	Alcoholism with delirium tremens	1	0	1	0
	Acute nephritis	1	0	0	1
	Abdominal actinomycosis, death due to surgical operation	1	0	0	1
	Subacute glomerular nephritis following burns	0	1	1	0
	Ruptured aortic aneurysm	1	0	0	1
2	Acute Cases Infectious				
	Lobar pneumonia	8	1	6	3
	Acute cerebrospinal meningitis	1	0	1	0
	Confluent bilateral bronchopneumonia	0	1	0	1
	Erysipelas	1	1	2	0
	Acute peritonitis	1	1	2	0
	Pyemia with multiple abscesses	0	1	1	0
	Empyema	1	0	1	0
	Acute endocarditis	2	0	1	1
3	Chronic Cases				
	Pulmonary tuberculosis	16	5	10	11
	Suprarenal tuberculosis	1	0	0	1
	Cardiovascular disease	20	10	19	11
	Syphilis	7	1	2	6
	Carcinoma	5	5	5	5
	Sarcoma	4	2	5	1
	Chronic infections (not tuberculous)	3	1	2	2
	Chronic wasting diseases (not tuberculosis or cancer)	1	2	3	0
4	Pregnancy	0	2	1	1
5	Obesity	0	1	1	0

showed that sections so prepared gave uniform slices of the colloid in the alveoli, while paraffin commonly gave such fractured sections of the colloid that satisfactory study of any peculiar appearances was prevented

## OBSERVATIONS

*Significance of Variation in the Color of the Thyroid Glands*—When the blocks were ready for cutting, they showed a variety of different

colors that had not been so distinct in the fresh material. It was possible to arrange the blocks in groups—cream colored, reddish amber, grayish yellow, gray-brown, tan-brown, grayish, yellow-amber, gray and brown—and it was expected that at least some of these color groups would correspond with some of the clinical groups. Comparisons were made by every means that could be devised, but it was impossible to correlate the color groups with the clinical groups, and it seemed therefore certain that the observed variations in color had nothing whatever to do with age, sex, race or morbid condition in the patients from whom the tissues were obtained at autopsy.

It had been suggested that variation in the appearance of the thyroid glands has something to do with the time of year at which they are collected. Nearly all these tissues were obtained during the months of December, January and February. As fifteen of them, collected during May, showed just the same variations, the suggestion of a relation between the variations in color and the time of the year was thought to be a mistake.

*Significance of Variations in Texture*—Some of the sections were soft and could be cut evenly and thinly, while others were hard and were cut with difficulty, the knife tending to ride over the tissue rather than to pass through it, so that only thicker sections might be prepared. A few of the sections were "gritty" apart from calcified blood vessels, which were rather frequent.

Although it was suspected that this hardness might be referred to overfixation or prolonged dehydration of the tissues, it seemed as though it might be due to some unknown inherent difference in the colloid. These differences were, therefore, carefully recorded and compared with the various clinical groupings. There was apparently no correspondence. Soft and hard tissues were found associated with all ages, both sexes, both races and all the disease groupings.

*Significance of Variations in Structure*—When the cut sections were examined with the naked eye, and then with a hand lens, forty-seven of them appeared to be similar, i.e., their substance was not divided up by noticeable connective tissue partitions, and it seemed to be made up of a parenchyma composed of alveoli of much the same general appearance, containing much the same average quantity of colloid of about the same uniform appearance. Under the microscope, these sections corresponded with the usual "textbook" pictures of the normal thyroid. It was tentatively assumed that this appearance was "normal," and that, on comparison of these apparently normal tissues with the clinical groupings, these glands would be found to have come from patients of about the same age who had died with much the same pathologic disturbances. This proved to be entirely erroneous. Thyroid glands of this "normal" appearance were found to have come from



patients from 1 month to 79 years of age, in proportions corresponding with the proportionate distribution of the total number of cases in each decade, of the whole number, twenty-six were from patients less than 50 years of age, twenty-one from patients more than 50 years of age, twenty-three were from patients between 40 and 70 years of age. The average age for the whole group of patients from whom these "normal

TABLE 3—*The Incidence of the Apparently Normal Thyroid Glands with Reference to the Diseases of the Patients from Whose Bodies the Glands Were Taken at Autopsy*

Causes of Death		Incidence of Apparently Normal Thyroid Glands
1	Acute Diseases	
	Infections	7
	Pneumonias	13
		— 20
2	Chronic Diseases	
	Cardiovascular renal diseases	13
	Tuberculosis	6
	Syphilis	5
	Carcinoma	2
	Sarcoma	1
		— 27
		47

TABLE 4—*The Incidence of the Thyroid Glands That Were Divided into Lobules by Distinct Fibrillar Partitions, with Reference to the Diseases of the Patients from Whose Bodies the Glands Were Taken at Autopsy*

Causes of Death		Incidence of Thyroid Glands Divided into Lobules by Fibrillar Partitions
1	Acute Diseases	
	Infections	4
	Pneumonias	5
		— 9
2	Chronic Diseases	
	Cardiovascular disease	3
	Tuberculosis	7
	Syphilis (with cardiovascular disease)	4
	Carcinoma	3
	Sarcoma	1
	Senile weakness after fracture (age of patient, 83)	1
	Amyotrophic lateral sclerosis	1
		— 20
		29

glands" came was 49 years. The glands were referable also to the sexes in proportions corresponding with the proportionate distribution of the total number of cases to each sex—male 36, female 12.

The disappointing results of the attempt to correlate these "normal" thyroid glands with the causes of death are shown in table 3.

Twenty-nine thyroid glands showed the structure to be divided into lobules by distinct and sometimes coarse fibrillar partitions. Our attempt to correlate these with the various groups was slightly more

successful. It is true this condition was observed in patients varying from 1 year to 83 years of age, but the average age was 50 years, and only seven persons were less than 40 years old, twenty-two being over 40. Of these, eighteen were males and eleven were females. Nineteen were white persons and ten black. The correlation of these thyroid glands with the causes of death is set forth in table 4.

Unlike the apparently normal thyroid glands, two thirds of the cases in which fibillar partitions occurred were definitely in the group of chronic diseases, though the classification was difficult, as one of the patients included in the group of those with chronic tuberculosis died of erysipelas, an acute infection, and one in the group of patients with bronchopneumonia, a person with a long-standing case of hemiplegia, may have had both syphilis and cardiovascular disease.

*Significance of Variations in the Appearance of the Colloid*—Under the microscope, the colloid was given careful attention, and was found to present a greater variation in appearance than was expected. The tissues were grouped, with respect to the appearance of the colloid, as follows:

- 1 The colloid in all the alveoli appeared to be uniform in substance
- 2 It differed in density (? color) in different alveoli
- 3 It was dense (dark colored) in occasional alveoli
- 4 Some of the colloid collections were laminated
- 5 The colloid was noticeably vacuolated
- 6 Many of the colloid collections contained large vacuoles
- 7 Many of the colloid collections contained great numbers of small vacuoles
- 8 The colloid appeared to be melting away at the edges of the collections

Each group was separately gone over with reference to age, sex, race and morbid conditions, as put down heretofore, but in not one could the peculiar appearance of the colloid be made to correspond with any given clinical condition. As nothing came of these attempts, it seems unreasonable to burden the reader with further details and tabulations.

*Significance of Variations in Alveolar Space*—There remained the investigation of the size of the alveoli. At first, with the eye as guide, the sections were grouped according to the following scheme:

- 1 The alveolar spaces contained no colloid substance
- 2 They contained little colloid
- 3 They contained unequal quantities of colloid
- 4 The size of the alveolar spaces and the quantity of colloid that they contained were fairly uniform in the same lobules, though they varied in different lobules
- 5 The alveoli contained an apparent excess of colloid
- 6 There were occasional small colloid cysts

As the sections were first gone over, it seemed easy to refer each to one or the other of these groups, but later, when section was compared with section, it was necessary to reassign many of them, and still later to make further changes, until it seemed that, except for groups 1 and 6, a satisfactory arrangement could never be made unless a method of measuring the alveoli could be adopted

It was then decided to make camera lucida tracings of representative fields of a section of each gland, in the hope that, by comparing these, some accurate grouping could be effected, but this also proved unsatisfactory. The tracings outlined the alveolar lumina, which almost invariably were filled or partly filled with colloid. It was obvious that the glands with many closely set alveoli contained a much greater proportionate volume of glandular space and colloid than did those with fewer and more widely separated alveoli. It also seemed probable that the average size of the alveoli varied much from gland to gland, although the frequent great variation in size within individual glands made the visual estimation of this uncertain. The study of these tracings next suggested that the measurement of the alveolar space as traced might make possible an interpretation of these variations. Thinking of the thyroid gland as a porous body containing many epithelium-lined spaces (the alveoli), we perceived that if we could determine the average size of the alveoli in a given portion of each gland, we could then calculate the proportion of each gland represented by the colloid-filled lumina—a sort of "index of porosity." Such measurements would be indicative of the relative amounts of colloid contained in the respective glands. These amounts obviously varied greatly. If values could be obtained, one could then decide whether this variation was correlated with age or with clinical pathologic groups. The most accurate method of arriving at such values would be by serial sections and reconstruction. This method, however, because of the tremendous amount of labor that it required, was out of the question. After careful consideration, we decided that an estimation of the percentage of alveolar area as seen within the tracings of the alveolar outlines in a given area of each gland would give an index of the proportion of alveolar lumen to total gland. Such a procedure would simply express in a numerical scale the variations in the microscopic sections and tracings, which were so obvious to the eye but so difficult to evaluate by the eye alone.

The following procedure was adopted. Camera lucida tracings from sections of each gland were carefully made, the pencil's point following the epithelial lining of the alveoli. These tracings were made at a standard magnification of 63.5 diameters. Each tracing was of a measured area—usually 20 square inches, which corresponded to an area of  $\frac{5}{4000}$  square inch of a microscopic section. In cases in which the picture was not uniform through the section, several or larger areas were traced to insure a representative picture. This gave us tracings of a measured representative area of each gland, showing the outline of the lumen of every alveolus in this area. The surface area of each alveolar space in these tracings was measured. The total area of each field being known, it was possible, by taking the sum of all the alveolar areas in each field and comparing this with the total area of the field, to determine the relative percentage of alveolar space and the relative percentage of intervening tissue. The average size of the alveoli was also determined for each gland by counting the number of alveoli and dividing the total alveolar space by this number.

The method of measurement was by superimposing paper, ruled to  $\frac{1}{400}$  square inch, on a tracing and counting the little squares within each alveolar outline. Such squares as were cut by the margins were counted if half or more fell within the outline. Before the adoption of this method, an attempt was made to measure

the areas within the alveolar outlines by use of a planimeter, but many were so small that accurate measurement could not be made with the available instruments. The results were not reduced to scale, because the purpose was not to determine absolute values but to obtain comparable values. The following is an example of the data obtained in the measurement of one gland in this way:

Total area traced	23.46 sq. in.
Number of complete alveoli	188
Number of incomplete alveoli (those cut by the margin of the tracing)	24
Sum of areas of complete alveoli	6.60 sq. in.
Sum of areas of incomplete alveoli	0.82 sq. in.
Total alveolar area (or "open space")	7.42 sq. in.
Percentage of alveolar open space	31.7
Percentage of intervening tissue	68.3
Average size of alveoli	0.04 sq. in.

Several comments should be made at this point concerning the data thus obtained. First, serial sections were not made in any cases, three or four sections being the most studied from any one gland, and all these being cut from one block of tissue. We cannot, therefore, determine mathematically the reliability of the data nor prove that the sections and tracings were representative. The sections, however, were taken from corresponding portions of the various glands, and tracings sufficiently large to be representative of each were made and measured. We believe that, granting a fairly large error, the data are sufficiently reliable to form the basis of the comparisons that follow. Secondly, it is well to recall just what was measured and what is meant by "alveolar space" or "alveolar open space." It was that area included within the traced alveolar outlines made by following the inner margin of the lining epithelium. In the tracings, only alveoli with definite lumina appeared. Empty alveoli without appreciable lumina were not traced or measured. This means that the intervening tissue was not always stroma, but included small empty alveoli, when present. This is well illustrated by the data on a gland from a 2 days old, probably premature, infant. The microscopic picture was that of a fetal thyroid gland without any alveoli containing colloid, and little connective tissue stroma. The alveolar open space was zero, the average size of the alveoli was zero, and the intervening tissue was 100 per cent. These data also show that the average size of the alveoli was based on those with definite lumina, almost invariably containing colloid.

Camera lucida tracings from 100 of the thyroid glands discussed in this paper were made and measured. For each gland, two values were finally calculated: (1) the percentage of alveolar open space, and (2) the average size of the alveoli.

The data obtained by measurement of the alveolar space are given in table 5. The first value is, as has been explained, an index of the glandular space. This factor would seem to be of importance, because it is known that the colloid stores iodine. For this reason, and because the value of this factor showed such wide variations (from 0.8 to 92 per cent), we thought that it might be correlated with age or with pathologic conditions found at autopsy.

TABLE 5—*The Percentage of the Alveolar Space and the Average Sizes of the Alveoli of Thyroid Glands Taken from Eighty-Three Patients at Autopsy*

Number	Age, Years	Alveolar Space, per Cent	Average Size*	Number	Age, Years	Alveolar Space, per Cent	Average Size*
1	2 days	0 0	0 0	51	50	54 4	9 8
2	1 mo	43 8	5 4	52	50	28 6	2 4
3	5	23 0	1 7	53	53	25 8	5 9
4	6	32 1	2 0	54	53	20 6	1 7
5	11	43 2	3 2	55	54	31 7	4 0
6	12	52 3	4 5	56	54	54 9	8 8
7	17	39 7	7 0	57	54	34 7	5 0
8	20	61 6	8 3	58	55	21 6	2 0
9	20	77 1	21 4	59	55	54 8	3 1
10	22	26 4	8 6	60	56	52 6	5 0
11	22	45 0	6 3	61	57	27 8	3 6
12	23	52 4	11 0	62	58	68 8	9 2
13	24	47 0	3 4	63	58	34 3	2 6
14	24	31 4	2 2	64	58	66 6	13 2
15	25	48 1	6 0	65	60	24 6	9 1
16	26	46 4	11 6	66	60	24 3	2 2
17	27	74 2	43 0	67	60	54 3	7 4
18	27	59 7	6 9	68	60	45 7	5 7
19	27	61 7	5 4	69	62	10 8	3 0
20	28	46 6	4 2	70	63	52 0	4 0
21	30	42 3	3 0	71	63	48 2	3 1
22	32	39 1	5 0	72	64	59 0	14 0
23	35	31 7	3 8	73	61	41 3	4 2
24	35	63 9	9 1	74	65	35 5	4 0
25	37	19 4	1 8	75	65	44 3	5 1
26	38	53 0	6 3	76	65	66 5	9 9
27	38	57 7	9 6	77	65	35 9	3 1
28	38	29 3	3 9	78	66	35 5	6 5
29	38	28 8	4 6	79	68	58 2	4 2
30	39	32 8	2 2	80	68	40 1	4 0
31	40	70 9	8 9	81	68	13 2	1 3
32	41	33 2	5 6	82	69	49 5	6 3
33	42	26 4	5 4	83	70	35 5	4 3
34	42	50 7	9 0	84	70	54 8	12 7
35	42	73 5	26 8	85	70	23 8	1 1
36	44	55 9	10 7	86	71	36 3	5 8
37	44	33 1	5 7	87	72	41 8	6 0
38	44	17 6	2 8	88	72	37 3	4 0
39	45	25 6	2 2	89	72	47 0	6 4
40	47	51 8	10 3	90	73	39 6	4 1
41	47	33 9	4 0	91	73	52 6	12 0
42	47	40 5	5 0	92	74	43 2	6 6
43	48	57 6	5 5	93	74	52 0	3 0
44	49	12 9	2 6	94	75	53 3	10 5
45	49	63 9	8 2	95	77	60 9	6 4
46	49	45 5	7 1	96	77	33 0	6 3
47	49	46 9	2 1	97	77	29 7	7 0
48	49	51 9	5 5	98	78	29 0	5 0
49	50	63 2	10 3	99	78	47 0	8 0
50	50	92 0	75 0	100	83	34 3	4 0

\* In hundredths of a square inch

In order to determine the presence or absence of any correlation between alveolar open space and age or disease, the data were analyzed according to the following rules

1 Determine the arithmetical mean for the whole series of 100 cases (the "series mean")

2 Determine the arithmetical mean of each of the groups (age groups, by decades, and disease groups)

3 Adopt the series mean from step 1 as the normal standard for comparison

4 Determine the difference between each group mean and the series mean

5 Calculate a significant difference for  $P = 0.05$  in each comparison, following Fisher's method,<sup>1</sup> by the formula

$$\text{Significant difference} = \frac{\sqrt{\frac{\xi d_1^2 + \xi d_2^2}{n_1 + n_2 - 2}} \times t}{\sqrt{\frac{n_1 \times n_2}{n_1 + n_2}}}$$

when— $\xi d_1^2$  = the sum of the squares of the deviations of the first series,

$\xi d_2$  = the sum of the squares of the deviations of the second series,

$n_1$  = number of observations in first series,

$n_2$  = number of observations in second series and

$t$  = factor from Fisher's table IV for  $P = 0.05$

6 Compare the "significant difference" as determined thus with the observed difference to estimate its probable significance

The calculation in step 5 gives the magnitude of a difference that is 95 per cent probable ( $P = 0.05$ ), that is, a difference of such a size as would occur by chance only once in twenty trials. This degree of probability is usually adopted as the limit of significance. Therefore, if a given observed difference is less than this calculated significant difference, it is not regarded as significant, but if it is equal to or greater than this figure, it is considered significant. In estimating the significance of the differences, the standard or probable errors of these differences could have been used, but it was thought that Fisher's method was more suitable because of the small number of observations.

In table 6, the mean percentage values for the alveolar open space for each decade are compared with the series mean (43.3 per cent). In the fourth column, the observed differences are given. By simple inspection of these, it was seen that, except for the first three decades, the differences were small. It appeared from superficial examination that, in the first decade, the mean value of the alveolar open space was decidedly less than the mean for the whole span of life. In the second decade, this value seemed to rise above the average and then to fall through the third decade to a level approximately equal to the series mean for the remainder of life. However, when these observed differences were compared with the calculated significant differences, it was seen that only in the case of the first decade did the observed difference equal or exceed the significant difference. For this decade there were only four glands, one of which (that of an infant, aged 2 days) gave a value of zero. In so small a series, this one value had an undue weight on the mean. Also, the case was questioned because of the probable prematurity of the infant. With this doubtful case omitted, the mean for this decade was 33.1, giving a difference from the series mean of

<sup>1</sup> Fisher, R. A. Statistical Method for Research Workers, London, Oliver & Boyd, 1925, p. 109

102 On recalculation, the significant difference of 18.1 was obtained. It was therefore evident, from table 6 and the considerations set forth, that our figures failed to show any significant variation of alveolar open space with relation to age. The reader will undoubtedly note that in the tables comparatively few cases are given for the early decades. The thyroid glands were collected from routine autopsies, without regard to age, because the investigation of variations in the thyroid gland with reference to age was not the primary object of the study.

TABLE 6—*Mean Percentages of the Alveolar Open Space in Thyroid Glands Grouped with Reference to the Ages of the Patients from Whose Bodies the Glands Were Taken at Autopsy*

Groups	Number of Cases	Mean	Difference from Series Mean	Significant Difference $P = 0.05$ (after Fisher)
Whole series	100	43.3		
Decade				
First	4	25.5	+17.8	16.1
Second	5	54.8	-11.5	14.1
Third	12	48.5	-5.2	9.3
Fourth	10	42.7	+0.6	10.4
Fifth	21	45.7	-2.4	7.7
Sixth	16	40.4	+2.9	8.5
Seventh	17	41.4	-1.9	8.5
Eighth	15	42.5	+0.8	8.3

TABLE 7—*Mean Percentages of the Alveolar Open Space in Thyroid Glands Grouped with Reference to the Diseases of the Patients from Whose Bodies the Glands Were Taken at Autopsy*

Groups	Number of Cases	Mean	Difference from Series Mean	Significant Difference $P = 0.05$ (after Fisher)
1 Tuberculosis	18	40.4	+2.9	8.0
2 Cardiovascular disease	31	45.2	-1.9	6.4
3 Acute infection	15	45.9	-2.6	8.5
4 Rapid deaths from other causes	5	33.3	+10.0	14.6
5 Tumors	17	45.6	-2.3	8.7
6 Chronic nontuberculous infection	4	51.8	-8.5	15.3
7 Chronic wasting diseases	6	41.6	+1.7	10.4
8 Syphilis	10	41.8	+1.5	10.3
9 Bronchopneumonia	29	41.9	+1.4	6.6

In table 7, the mean percentages of alveolar open space for the disease groups are compared with the series mean. Here the differences between the group means and the series mean were small, except in groups 4 and 6. However, even in these groups, the observed differences (column 4) were much smaller than the calculated significant differences (column 5). The percentage of alveolar open space obviously was not correlated with the disease groups given. Further analysis of the larger groups by subdivision into decades, as was done for the whole series, failed to show any variation with age within these groups.

The analysis of our data to this point failed to reveal any significant variation in percentage of alveolar open space in relation to age or

pathologic condition. As a further check, the 100 cases of the series were grouped in a frequency table according to percentage of alveolar open space, an interval of 10 and the midrange values of 5, 15, 25, etc., being used. The results are shown in table 8. Eighty-eight of the glands fell in the groups from 25 to 65, inclusive. In the third column of the table, the average ages for these groups are given. They all fell in a range of five years. The average age for the whole series was

TABLE 8—*The Average Ages for Different Percentages of Alveolar Open Space*

Percentage Alveolar Open Space Midrange Values	Number of Cases	Average Age, Years
5	2	
15	5	
25	16	47.4
35	21	51.5
45	21	47.5
55	21	51.4
65	9	52.1
75	1	
85	0	
95	1	

TABLE 9—*The Average Size of the Alveoli in Thyroid Glands Grouped with Reference to the Age and the Diseases of the Patients from Whose Bodies the Glands Were Taken at Autopsy*

Group	Number of Cases	Mean	Probable Error	(B) Probable Error of		
				(A) Difference	Difference	A - B
Whole series	100	7.1	1.3			
First decade	4	2.3	1.8	4.8	3.1	1.5
Second decade	5	8.0	2.9	1.8	3.1	0.6
Third decade	12	9.3	2.5	2.2	2.7	0.8
Fourth decade	10	5.5	1.7	1.6	2.0	0.8
Fifth decade	21	10.3	1.9	3.2	2.2	1.5
Sixth decade	16	5.5	1.6	1.6	2.0	0.8
Seventh decade	17	5.3	1.6	1.8	2.0	0.9
Eighth decade	15	6.3	1.3	0.8	1.6	0.5
Tuberculosis	18	5.0	2.5	2.1	2.7	0.8
Cardiovascular renal disease	31	6.2	2.2	0.9	2.0	0.5
Acute infection	15	9.3	2.5	2.2	2.7	0.8
Rapid deaths	5	5.2	2.6	1.9	2.8	0.7
Tumors	17	10.9	2.0	3.8	2.3	1.7
Chronic nontuberculous infection	4	5.2	5.3	1.9	5.4	0.4
Chronic wasting diseases	6	4.9	1.4	3.2	1.8	1.8
Syphilis	10	7.3	1.7	0.2	2.0	0.1
Bronchopneumonia	29	7.5	1.9	0.4	2.2	0.2

47.8 years, which is close to all the group values. This was added evidence of the lack of a correlation between percentage of alveolar open space and age.

The determination of the relative sizes of the alveoli also proved to be of no significance. The variations in size within each gland resulted in large errors for the mean values. These errors in conjunction with those of the group and series means robbed the results of all significance. Table 9 gives the mean alveolar sizes for the series and the groups, by decades and diseases. The means and the probable errors of the means (calculated as 0.67 of the standard deviations) are given in columns 3



and 4 The observed differences from the series mean are shown in column 5 with the probable errors of the differences in column 6 In no case did the observed difference between the series mean and a group mean equal twice the probable error of the difference This is shown in the last column, the figures of which were obtained by dividing the observed differences by the probable errors of these differences This indicates a lack of significance in the differences measured by a less exacting standard than that used in treating the percentage of alveolar open space Fisher's method, which would serve only to emphasize this lack of significance, was not applied to these data because it would have been a needless expenditure of time to do so

### CONCLUSIONS

A preliminary study of 100 thyroid glands was made for the purpose of determining whether variations in their histologic appearances could be referred to age, sex, color or disease in the persons from whom they were obtained

Color variations in the blocks of fixed tissue were marked, as was also the ease or difficulty with which they could be cut, but none of these characteristics could be correlated with the clinical conditions of the patients from whom the tissues came

The "textbook" appearance was shown by sections of forty-seven of the glands Although it was expected that they would have come from the bodies of patients of about the same age who died of similar diseases, they were found to be from bodies of patients of all ages and of a variety of morbid states

Twenty-nine glands showed connective tissue trabeculation Of these, twenty came from bodies of patients who had died of chronic diseases and only nine from the bodies of those who had died of acute diseases

Numerous variations in the appearance and condition of the colloid were studied, but not one could be found to correspond with any pathologic condition of the patient

A method was devised by which it was possible to measure the alveolar space, both on the average and in the aggregate, but a statistical analysis of the data so obtained failed to show any correlation with age or disease groups

As the study of 100 cases by these various means showed nothing, it was not considered worth while to continue the research

The results indicate that, with the single exception that chronic disease of the patient frequently leads to trabeculation, the grosser histologic variations of the thyroid gland in man do not afford any information with respect to the age, the sex, the color or the morbid condition of the patient

# THE BLOOD PLATELETS IN TYPHUS FEVER \*

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There is at present an uncertainty regarding the form of the virus of typhus fever in the blood stream, but strong evidence exists that the virus is represented by *Rickettsia prowazeki*. Since the rickettsiae associated with heartwater disease<sup>1</sup> and Rocky Mountain spotted fever<sup>2</sup> have been demonstrated free in the blood stream, it is reasonable to suppose that *Rickettsia prowazeki* may be similarly distributed. However, from the results of early experimental studies on typhus fever, it was believed that the virus was intimately associated with the circulating blood cells, either the leukocytes or the platelets.

The observations of several investigators indicated that the virus of typhus fever was closely associated with the blood platelets. Kusama,<sup>3</sup> in 1919, was led to this conclusion by the fact that the platelets obtained from the blood of a monkey suffering from experimental typhus fever induced typhus fever when injected into a normal monkey, but that the supernatant plasma from the same sample of blood failed to do so. To demonstrate that the virus was actually contained in the platelets and not merely simultaneously sedimented by virtue of a similar specific gravity, he ground the platelets with the powder of a filter candle.<sup>4</sup> After half an hour's centrifugation, following this procedure, it was found that the supernatant fluid induced typhus fever in monkeys. Kusama concluded from this experiment that the virus was present in the platelets and was liberated by the process of grinding.

Ségal<sup>5</sup> and Arkwright and Bacot<sup>6</sup> concurred in the opinion that the virus of typhus fever is intimately connected with the blood platelets, and that a high concentration of the virus can be realized in the platelet sediment by the centrifugation of citrated blood.

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From the Department of Medicine, Peking Union Medical College

1 Cowdry, E V J Exper Med **42** 231, 1925

2 Reimann, H A J Infect Dis **43** 93, 1928

3 Kusama, S Japan M World **1** 125, 1920

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## THE PLATELETS IN TYPHUS FEVER

Reports of the behavior of the blood platelets during typhus fever are scarce. It therefore seemed of value to make a series of observations on patients with typhus fever to ascertain whether the platelets respond in the usual way to an acute febrile disease or in a manner peculiar to typhus fever. The present paper states the results of observations on the fluctuation of the number of the platelets during typhus fever. Experimental studies regarding the relationship between the platelets and the virus of typhus fever are also described.

*Method*—The platelets were counted by the direct method. A modification of Thomsen's technic, described in detail elsewhere,<sup>7</sup> was used. Briefly, the method comprised the following procedures. Blood was drawn from a vein into a small syringe containing citrate solution. The citrated blood was allowed to sediment. The sedimentation permitted the red cells to settle, while the platelets remained in homogeneous suspension in the supernatant plasma. The platelet suspension was then suitably diluted with physiologic sodium chloride solution containing a trace of formaldehyde, it was then placed on the hemocytometer slide and counted. By calculation, the number of platelets per cubic millimeter of blood could be reliably estimated. Normal human blood, according to this method, contained approximately 350,000 platelets per cubic millimeter.

*Platelet Counts*—The clinical material used in this study was obtained at the time of an outbreak of an epidemic of typhus fever among Chinese military prisoners during the winter of 1928. Thirteen patients were studied. Their cases were uncomplicated and of moderate severity. It was not always possible to ascertain precisely the date of onset of the disease in each case, most of the patients, however, came under observation on about the fifth day of the illness. The average duration of the febrile period was fifteen days. Platelet counts were made, as a rule, every other day during the early period and at longer intervals during convalescence.

The curves made by charting the various platelet counts were, in most cases, similar in form. As in other acute febrile diseases of comparatively short duration, a thrombopenia occurred during the febrile period, followed, during convalescence, by a rise toward the normal level. In three cases, the number exceeded the normal level, that is, a transient thrombocytosis occurred. Chart 1 shows an example of this type of curve.

The thrombopenia was usually more pronounced and the subsequent increase in the number during convalescence was markedly delayed in typhus fever in contrast with the behavior of the platelets during lobar pneumonia.<sup>7</sup> In five patients, the number never attained the normal level during observation over a period of from twenty-six to thirty-seven days. In five, after the number had increased slightly following the initial thrombopenia, it again fell to a level of about 200,000, at which it remained until the patients left the hospital. A curve of this nature is illustrated in chart 2. An unexplained peculiarity was observed in nearly all the cases and is illustrated in charts 1 and 2. It was the tendency toward a second phase of thrombopenia following the initial increase in number.

The lowest count observed, 8,000 per cubic millimeter, occurred in a patient on the seventh day of the disease. In this instance, the platelet suspension (after

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7 Reimann, H. A. J. Exper. Med. **40** 553, 1924.

sedimentation of the blood) was placed directly on the slide, without dilution, and the platelets counted. In this patient, the number subsequently increased slowly and reached only 168,000 per cubic millimeter on the twenty-first day of convalescence.

*Comment*—In general, it may be stated that contrary to the observations made by Pletnew,<sup>8</sup> no distinct relationship between the severity

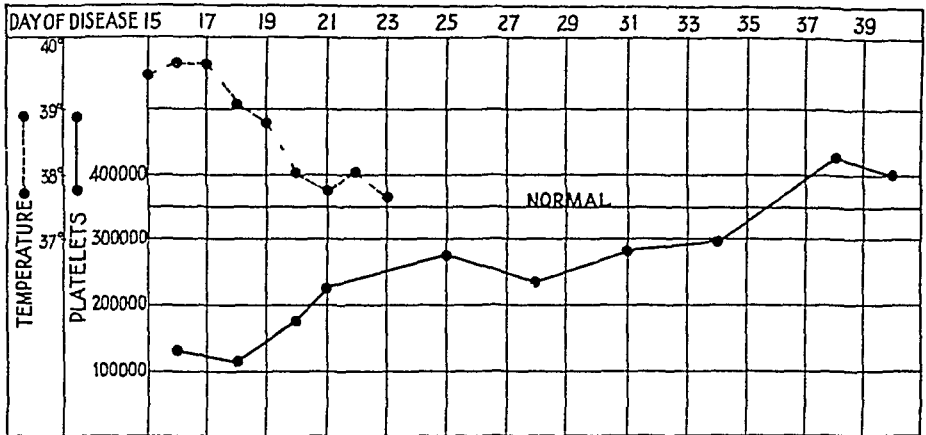


Chart 1—The blood platelet curve in a case of typhus fever, showing thrombopenia in the febrile period and a transient thrombocytosis during convalescence

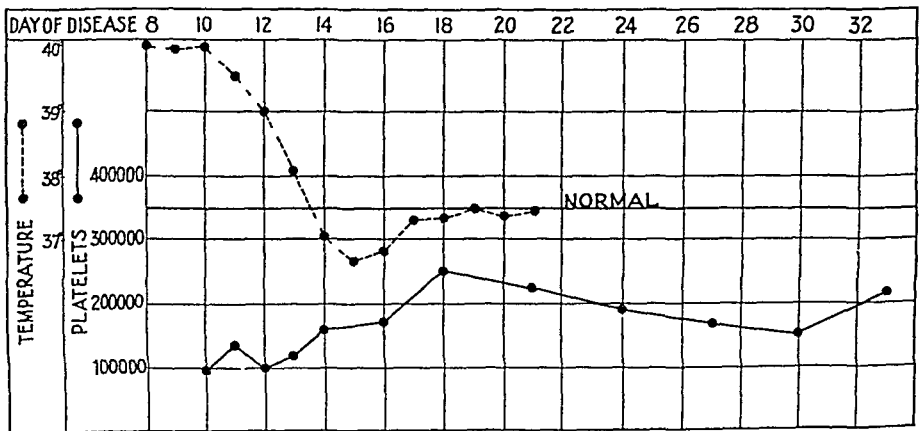


Chart 2—The blood platelet curve in a case of typhus fever. The curve shows a prolonged thrombopenia.

of the illness and the degree of the thrombopenia was recognized. Neither did there seem to be any association between the presence and the severity of the exanthem and the number of the platelets. Epistaxis and a tendency to bleed from the gums was observed only in the patient showing the extremely low count.

## THE RELATIONSHIP BETWEEN THE VIRUS AND THE PLATELETS

An experimental study was made to determine whether or not the virus (*Rickettsia prowazekii*) was free in the blood stream or contained in the platelets. Blood from patients with typhus fever and from experimentally infected guinea-pigs was used.

*Methods*—A stock strain of the virus of typhus fever in animals was started by the injection of 5 cc of patients' blood, taken on the eleventh day of illness, into the peritoneal cavity of a guinea-pig. Thereafter, for propagating the virus, the method of Weil and Breml<sup>9</sup> was adopted. Briefly, the technic was as follows. From five to ten days after inoculation with the typhus fever virus, the guinea-pigs developed a typical fever, which lasted from seven to nine days. On the fourth day of the fever, an animal was killed, and the brain was removed aseptically and emulsified in 20 cc of physiologic solution of sodium chloride, 1 cc of this emulsion was used for further inoculation. All animals were inoculated intraperitoneally. On several occasions during the passages of the virus, sections were made of a portion of the brain used for the transfer, and the characteristic histologic lesions of typhus fever were found. Tests of immunity to verify the specificity of the fever were also made in those cases in which this procedure was indicated, by allowing a period of at least two months to elapse from the time the animal recovered from the first fever before reinoculating it with known typhus virus. The animal was considered immune if fever failed to develop within thirty days after the reinoculation.

Platelets from human blood were obtained by running from 20 to 50 cc of blood into an equal amount of a 10 per cent solution of sodium citrate in physiologic sodium chloride solution. The mixture was centrifugated at slow speed for ten minutes. The erythrocytes and leukocytes thus formed a sediment, leaving the platelets in suspension in the supernatant plasma. The platelet suspension was then centrifugated at 3,300 revolutions per minute for one hour. The clear supernatant fluid was removed, and the platelets were resuspended in a small amount of physiologic sodium chloride solution. A sediment of cells was not obtained by further centrifugation of the clear plasma.

Platelets were obtained from guinea-pigs in a similar manner. The blood was withdrawn from the heart and immediately mixed with the citrate solution.

*Experiments with Human Blood*—Blood specimens from thirteen patients were treated in the manner described. As a rule, 50 cc was withdrawn, and the platelets obtained from this amount was resuspended in 1 cc of physiologic solution of sodium chloride. Portions of this suspension and 10 cc amounts of the diluted clear plasma were then injected, respectively, into guinea-pigs in two separate series. Several of the animals receiving the plasma died shortly after the injections.

Of the ten animals surviving the injection of the plasma, seven showed the characteristic typhus fever reaction, and proved immune to subsequent reinoculation. The remaining three animals failed to develop fever following the injection of the plasma, but after reinjection of known virus two months later, they developed typhus fever.

All but two of the thirteen guinea-pigs inoculated with the platelets developed typical typhus fever. One of the two died before the reinoculation, the other developed typical typhus fever after reinoculation with virus from the brain three months later. Apparently, the percentage of animals successfully infected was about the same whether the platelets or the clear cell-free plasma was used.

Another experiment was then made by allowing 10 cc of blood from a patient with typhus fever to clot and then separating the serum by centrifugation at high speed for twenty minutes. The clear cell-free serum was divided into three 15 cc lots, and these were injected intraperitoneally into three guinea-pigs. Two of the three animals developed typical typhus fever ten days later. The third was apparently not infected.

*Comment*—The experiments with human blood indicate that the virus of typhus fever exists free in the plasma and is not necessarily associated with the formed elements of the blood.

*Experiments with Guinea-Pig Blood*—The methods employed in the experiments with human blood were used. Blood to the amount of 20 cc was obtained from a large guinea-pig on the fourth day of experimental typhus fever. One half of the blood was received into an equal amount of citrate solution, and centrifuged as usual, so that the platelets were suspended in the supernatant plasma.

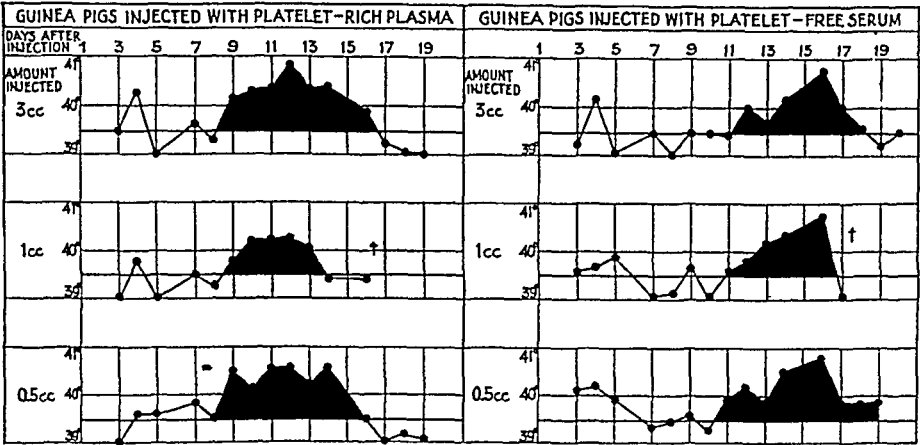


Chart 3—The temperature reactions of two groups of guinea-pigs one of which had received injections of platelet-rich typhus fever plasma and the other, injections of platelet-free serum. Typhus fever of similar severity was induced in each group. † indicates death.

The other half of the blood was allowed to clot. Three normal guinea-pigs were inoculated with 0.5 cc, 1 cc and 3 cc of the platelet-plasma suspension, respectively, and three were inoculated with corresponding amounts of the platelet-free serum derived from the same sample of blood. The results are shown in chart 3.

*Comment*—It is evident from the reactions of the animals that both the platelet-rich plasma and the platelet-free serum induced typhus fever of similar severity.

SUMMARY AND CONCLUSION

From the results of observations and experiments in this study, evidence is presented against the view that the blood platelets contain the virus of typhus fever or that the two factors are closely associated. The fluctuation in the number of blood platelets in patients during typhus fever, though similar to that observed in other febrile diseases,

is somewhat peculiar as compared with the changes usually observed in other acute febrile diseases. The thrombopenia is usually more pronounced, the subsequent return to the normal number is retarded and a tendency to a secondary thrombopenia usually occurs. This unusual behavior may be attributed to two factors. 1 Typhus fever is usually of longer duration than some of the diseases in which the platelet count has been followed (e g, lobar pneumonia). 2 The lesions of the disease chiefly affect the blood vessels. It can scarcely be admitted that the variations in the number of platelets during typhus fever indicate any connection between the platelets and the virus of the disease.

Experimentally, the platelet-free plasma and serum produced typical typhus fever reactions in guinea-pigs about as regularly as did the platelet suspension. The specificity of the reactions was repeatedly verified by tests for immunity, by transference of the disease to fresh animals and by examination of sections of the brain. From these observations, it would seem that the virus exists free in the blood stream, although attempts to demonstrate *Rickettsia prowazekii* in this study by staining were not successful. It is possible that a similar specific gravity of the platelets and the virus may account for the concentration of the virus in the sediment of platelets after centrifugation, which several observers have reported.

We conclude, therefore, that an association does not exist between the blood platelets and the virus of typhus fever and that the latter exists free in the blood stream.

# EXPERIMENTAL STUDIES ON THE RETICULO- ENDOTHELIAL SYSTEM

## IV EFFECT OF HORMONES ON THE ELIMINATION OF BILIRUBIN <sup>1</sup>

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AND

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The work of Mann and Magath <sup>1</sup> and others has drawn attention to the rôle of the reticulo-endothelial cells in the production of bilirubin. On the other hand, Melchior, Rosenthal and their co-workers <sup>2</sup> still maintain that the main organ in the production of bilirubin is the liver. They do not exclude, however, the reticulo-endothelial cells from the elements which are capable of transforming hemoglobin derivatives into bile pigment.

Experimental work in our laboratory <sup>3</sup> has shown that the function of the reticulo-endothelial cells can be stimulated by hormones. Others (Leites and Riabov <sup>4</sup> and Jaffe <sup>5</sup>) have confirmed this fact.

The following studies have been made to determine whether the elimination of bilirubin can be influenced by various hormones if the latter are given simultaneously with the injection of bilirubin.

Blood serum was obtained by centrifugation and a double volume of acetone was added. After a second centrifugation a clear solution was obtained, which was a faint yellow. This solution was compared colorimetrically with a standard solution of potassium bichromate.

### EXPERIMENTAL DATA

Experiments on rabbits showed that there is only a small amount of bilirubin present in the blood normally, and as there is little, if any, variation in this amount it was decided to disregard the physiologic bilirubin of the blood serum in the experiments.

One centigram of pure bilirubin dissolved in slightly alkaline water was injected into the vein of an ear, and blood was examined with the

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<sup>1</sup> Submitted for publication, Nov 19, 1928

<sup>2</sup> From the Department of Laboratories, United Israel Zion Hospital, Brooklyn

<sup>1</sup> Mann and Magath. *Tr. Sec. Path. & Physiol.*, A M A, p 29, 1921

<sup>2</sup> Melchior, Rosenthal and Licht. *Arch. f. exper. Path. u. Pharmacol.* **4** 28, 1922, *Klin. Wchnschr.* **1** 2265, 1922

<sup>3</sup> Goldzieher, M. A., and Hirschhorn, L. *Reticulo-Endothelial System. Influence of Hormones*, *Arch. Path. & Lab. Med.* **4** 958 (Dec.) 1927

<sup>4</sup> Leites, S., and Riabov, A. *Ztschr. f. d. ges. exper. Med.* **59** 709, 1928

<sup>5</sup> Jaffe. *Ztschr. f. d. ges. exper. Med.* **62** 538, 1928



colorimeter at intervals. The concentration of the bilirubin in the blood was figured in the following manner:

Because of the size of our animals, the quantity of blood in a rabbit was put at 100 cc, in conformity with the generally accepted data. Thus, 1 cg of injected bilirubin was diluted 10,000 times. The addition of a double volume of acetone to the serum raised the dilution to 1:30,000.

Repeated experiments on ten animals showed that the rate of elimination of the bilirubin injected remained the same in the same animal. Variations were negligible and ranged from 0 to 6 per cent. On the other hand, if the time of elimination in the different animals was compared, considerable variations could be established. Fifteen minutes after the injection the bilirubin was either entirely eliminated or only a small part was retained in some animals. In other animals, if the test was also made after fifteen minutes, from 15 to 25 per cent was found to be still present, and in a third group the retention at the end of fifteen minutes was still from 50 to 60 per cent of the quantity injected. In the later stages, the bilirubin disappeared gradually from the blood of all the animals and in two or three hours even the slowly eliminating animals were practically free from it.

Because of the different speeds of elimination, the animals can be divided into three groups: (1) quickly eliminating animals, which eliminated from 100 to 90 per cent within fifteen minutes, (2) animals eliminating from 85 to 75 per cent in the standard time of fifteen minutes, (3) slowly eliminating animals which eliminated less than 75 per cent in fifteen minutes.

We had thirteen animals in the first, seven in the second and four in the third group. In these twenty-four animals, the effect of hormones was tried on the elimination of bilirubin.

The hormones used were epinephrine, solution of pituitary, a thyroid preparation, insulin and interrenin<sup>6</sup> (the hormone of the supra-renal cortex). The doses given were epinephrine, 1 cc of 1:4,000 solution, solution of pituitary, 1 cc of 1:10 solution, a thyroid preparation, 0.5 cc of the stock solution, insulin,  $\frac{1}{2}$  unit, interrenin, 0.5 cc of 1:20 stock solution.

It seems that three hormones, namely, epinephrine, solution of pituitary and insulin, have a similar effect on the quickly eliminating animals, as only from 57.5 to 67 per cent of the bilirubin was eliminated, instead of the 96 per cent in the previous control experiments. The effect of these hormones is less marked in the intermediate group. Thus, epinephrine seems to accelerate the elimination slightly (from 81 to 86 per cent), whereas solution of pituitary and insulin accelerated from 80 to 90 and 95 per cent, respectively.

<sup>6</sup> Goldzieher, M. A. *Klin. Wchnschr.* 7:1124 (June) 1928, *The Adrenals*, New York, The Macmillan Company, 1928.

In the group of slowly eliminating animals, the effect is pronounced and just opposite to that in the first group. The elimination is accelerated by epinephrine, solution of pituitary and insulin from 54 to 90, 88 and 85 per cent, respectively. The two other hormones are decidedly different in their effect. Interrenin is exceedingly effective with the slowly eliminating animals, as the elimination is accelerated from 53 to 93 per cent. In the quickly eliminating group, as well as in the intermediate group, the effect of interrenin is practically nil. In marked contradistinction to all the other hormones, a thyroid preparation has practically no effect on elimination, and this holds true for all three groups of animals.

The next step was to determine whether the formation of bilirubin from laked blood could also be influenced by the same hormones. To this end a series of white rats received intravenous injections of laked blood of a sheep, 3 cc of blood was injected, and twenty-one hours later samples of blood were examined for the presence of bilirubin. It seems that the rate of the formation of bilirubin in the rats injected with hemoglobin varies individually. Taking an average figure, it appears that a normal rat produces, in the standard time of twenty-one hours after injection, 1.75 units of bilirubin. The differences downward and upward range between 1.4 and 2.2 units.

Rats into which were injected laked blood were given hormones, the hormones being injected twice on the day that the blood was injected and again on the morning of the following day. The sample of blood for estimating bilirubin was taken one hour after the last injection.

Normal animals that had received a solution of pituitary, epinephrine or a thyroid preparation showed an average figure of 1.7 and 1.9, respectively, which does not differ materially from the normal average. The variations were distributed over a far greater range, namely, in the injections of a solution of pituitary, from 0.5 to 2.5, in the experiments with epinephrine the results varied from 1 to 3, and in the thyroid group from 0.5 to 3.5.

More conspicuous differences were brought out in the experiments with insulin and interrenin, as averages were 1.1 and 2.7, respectively. In other words, less bilirubin was found after the administration of insulin and considerably more after interrenin had been given. The individual variations in the experiments with insulin ranged from 0.2 to 2, while in the interrenin group, the figures ranged from 1.25 to 5.

The results of these experiments are difficult to interpret, as they represent most probably the effect of the hormones on both the formation and the elimination of bilirubin. In view of the fact that the specimens of blood were taken one hour after the last injection of hormones, it seems probable that the excessive or decreased production of bilirubin

accounts for the different results. At least the first series seems to show that the effect of hormones on elimination subsides within an hour.

In referring to previous experiments, as well as to the observations of others, one may recall the marked stimulating or inhibiting effect of hormones on the reticulo-endothelial system. We are inclined, therefore, to suggest that the results of the second series indicate an effect of hormones on the reticulo-endothelial system in the production of bilirubin from hemoglobin.

In a third series of experiments, the attempt was made to study whether the hormonal interference with the reticulo-endothelial cells is also effective if jaundice was due to some hemolytic poison. In this experiment nine rabbits were injected repeatedly with 5 cc of a 1:500 solution of phenylhydrazine. The injections were given subcutaneously on three consecutive days, once a day, and on the fourth day a sample of blood was taken for examination. The quantity of bilirubin demonstrated in this sample was low in spite of the development of marked anemia. The animals were left alone for two weeks until they seemed to recuperate, and then the injection of phenylhydrazine was repeated with simultaneous injections of hormones. The results obtained were not satisfactory, as the quantities of bilirubin in both the control experiments and the hormone experiments were too small to allow of comparison. It is possible that the same experiment might yield more valuable results if another hemotoxin was chosen or a more suitable procedure used.

#### COMMENT

The experiments have shown that the elimination of bilirubin injected into animals is subject to variations which seem to depend on a constitutional factor. Thus, the animals belong to two groups, which may be called the quickly and the slowly eliminating groups. Other animals range in between the two main groups.

We do not know the factors which account for the constitutional differences in the elimination of bilirubin, yet the following explanation might be suggested. Our experiments have established a stimulating or inhibiting effect of hormones on the elimination of bilirubin. We also claim that such an effect of hormones is due to the interference with the function of the reticulo-endothelial cells. Hence, we should conclude that physiologic elimination of bilirubin is also regulated by the action of the endocrine glands on the reticulo-endothelial system and perhaps also on the liver. The constitutional differences between the various animals would express a different state of the endocrine balance, which is upset by the additional administration of hormones, with the result that retardation occurs in the quickly eliminating group and acceleration in the slowly eliminating group. It is a prevailing con-

ception that the hormones can be grouped into antagonists and synergists such as, for instance, epinephrine on the one hand and insulin on the other. Such antagonism between the various hormones is not demonstrable in the effect of the substances on the function of the reticulo-endothelial system.

The evidence offered that hormones also influence the production of bilirubin is less unequivocal, yet it seems that there are changes of bilirubin formation due to the effect of injected hormones. This would suggest that the endocrine glands exert influence on this phase of intermediary metabolism and that endocrine disturbances may play a rôle in certain types of jaundice.

That hormones have a certain influence on the course of jaundice has been proved before, at least, so far as insulin is concerned. It has been shown by Echauz,<sup>7</sup> Bamberger<sup>8</sup> and others that the administration of insulin is instrumental in decreasing jaundice as to both its intensity and its duration. Insulin therapy in acute hepatic conditions, of course, has been introduced on the basis of different considerations. When injected simultaneously with dextrose, insulin was supposed to alleviate the disturbances of the carbohydrate metabolism, but at the same time its effect on jaundice became visible.

Our results show that insulin was the most active hormone in decreasing the formation of bilirubin and seem to bear out the empiric clinical observations.

#### CONCLUSIONS

Constitutional differences in the rate of the elimination of bilirubin are established in normal animals. Injections of hormones influence the rate of the elimination of bilirubin, and hormones seem to influence the formation of bilirubin.

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7 Echauz, F. *Arch. de med. cir. y espec.* **26** 558 (April) 1927.

8 Bamberger, J. *Deutsche med. Wchnschr.* **53** 1690 (Sept.) 1927.

# General Review

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## MULTINUCLEATED GIANT CELLS

WITH PARTICULAR REFERENCE TO THE FOREIGN  
BODY GIANT CELL \*

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### Introduction

### Varieties of Multinucleated Giant Cells

- Langhans' Giant Cell
- The Foreign Body Giant Cell
- The Osteoclast
- The Megakaryocyte
- Muscle Giant Cells
- The Giant Cells of Nerve Tissues
- Syncytial Giant Cells
- True Tumor Giant Cells
- Summary on Varieties of Giant Cells

### Cells from Which Giant Cells Have Been Reported to Develop

- Origin of Giant Cells from Fixed Connective Tissues
- Origin of Giant Cells from Tubular Epithelium
- Origin of Giant Cells from Surface Epithelium
- Origin of Giant Cells from Alveolar Epithelium
- Origin of Giant Cells from Serosal Mesothelium
- Origin of Giant Cells from Fixed Endothelium
- Origin of Giant Cells from Exudative Cells
- Origin of Giant Cells from Wandering Cells of the Tissues

### Theories of Formation of Giant Cells

- Nuclear Proliferation
- The Formation of Giant Cells by Fusion of Cells
- Formation by Combined Nuclear Multiplication and Fusion
- Additional Theories of the Formation of Giant Cells

### Methods Used in Studies of Giant Cells

- Fresh Preparations
- Sections of Fixed Tissues
- Vitally Stained Tissues
- Experimental Studies
- Tissue Cultures
- Reconstruction

### Functions of Giant Cells

### Fate of Giant Cells

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\* Submitted for publication, July 18, 1928

From the William H. Singer Memorial Research Laboratory of the Allegheny General Hospital

## Occurrence of Giant Cells

In Simple Granulation Tissue

In Areas of Degeneration, About Deposits and in Foci of Necrosis  
About Foreign Bodies

In Tuberculosis

In Syphilis

In Miscellaneous Granulomas

In the Vicinity of Animal Parasites in Body Tissues

In Giant Cell Granulomas of the Peritoneum

In Inflammatory Lesions of the Bones and the Joints

## The Giant Cells in Tumors

Occurrence of Giant Cells in Tumors of the Bone

Giant Cells in Tumors Other Than Tumors of the Bone

Epithelial Tumors

## Critical Conclusions

## INTRODUCTION

Large multinucleated giant cells are widely distributed in the tissues, in the physiologic and pathologic processes of which they play an important rôle. They appear to fall into two fairly well defined groups. In one group are the multinuclear tissue type cells arising by atypical nuclear division, and associated with proliferative processes generally. In the other group are one or more varieties of large, round or oval multinucleated cells, associated with inflammatory reactions and found about insoluble substances and foreign bodies. It is with the latter group that this review is chiefly concerned.

Faber<sup>97</sup> credited Johannes Muller,<sup>271</sup> who published a treatise on tumors in 1838, with the first description of foreign body giant cells. Robin<sup>99</sup> noted their presence in bone tissues in 1849. Paget<sup>276</sup> discussed them in his lectures in 1853 and Virchow<sup>370</sup> devoted considerable attention to them in his *Cellularpathologie* published in 1858. Langhans wrote an exhaustive thesis on giant cells in 1868, and his comprehensive interpretation of their origin, nature and distribution was justly recognized by the application of the name "Langhans' giant cell" to the cell in question. Following the article by Langhans the interest in giant cells developed rapidly, and a great many papers appeared, dealing chiefly with their origin, significance, diagnostic importance, similarities and differences. Between 1870 and 1900, there occurred an enormous number of contributions. Between 1900 and 1920, a much smaller number were forthcoming although the interpretation of the nature of these cells seems to have undergone its greatest development during this time. Since 1920, the advent of vital staining and vitally stained tissue cultures seems to have revived interest in them and many valuable contributions have appeared recently. In short the literature on giant cells parallels the entire history of the development of microscopic anatomy and pathology, including as it does the days of the blastema.

theory with its "mutterzellen" and the present day period of the development of lesions in vitro by vitally stained cells under the influence of vitally stained bacteria as irritants. It is my hope, in this review, to bring out most of the views about giant cells, and to incorporate a sufficient number of articles to support the statements, the literature is so extensive and so involved that a claim of completeness in any sense may not be made.

#### VARIETIES OF MULTINUCLEATED CELLS

The early observers discovered the presence of giant cells in many widely varying lesions and assumed that they would be found to differ more or less with the nature of the disease, with the type of tissue involved and perhaps even with the species of animal under examination. Robin<sup>307</sup> and Kolliker<sup>196</sup> found them in bone, Virchow<sup>350</sup> found and classed together similar structures in tubercles, in muscles undergoing repair and in nerve tissues. Weigert<sup>371</sup> stated that tubercle giant cells with peripherally arranged nuclei were to be found not uncommonly in sarcomas, and that, conversely, sarcoma giant cells with centrally placed nuclei were to be found in tuberculosis. When it is recalled in addition to the morphologic differences and the unusual distribution of multinucleate cells, that histologic technic was in its infancy, it is not surprising that great confusion arose and that some writers spoke of the cells as separate entities, while others classed them all together as a single type of cell. The confusion, for the most part, no longer exists, though there is at present no uniformity of opinion about the various types of tumor giant cells. It seems advisable to make a preliminary discussion of the various kinds of giant cells as they have been classified, namely the Langhans giant cell of tuberculosis, the foreign body giant cell (including those found in tumors and granulomas), the osteoclast, the megakaryocyte, the muscle giant cell, the giant cells of nerve tissues, the true epithelial syncytia and the various true tumor giant cells.

*Langhans' Giant Cell*—Langhans,<sup>211</sup> in 1868, appears to have been the first to devote an entire paper to the discussion of giant cells. He reviewed the literature then in existence and referred to Rokitsky<sup>307</sup> and his theory of "mutterzellen", to Virchow,<sup>350</sup> who first described the early tubercles of the peritoneum and omentum, to Robin<sup>305</sup> and his "myeloplaxes", to E. Wegner,<sup>368</sup> who described giant cells in tubercles of the liver, to Busch,<sup>61</sup> who found them in the choroid, to Bredichin,<sup>48</sup> who thought that they were formed in bone by the flowing together of several cells, and to Rindfleisch,<sup>303</sup> who thought that they came from endothelium of the lymph spaces. He also mentioned Buhl,<sup>55</sup> Deichle,<sup>81</sup> Colberg<sup>70</sup> and Manz<sup>248</sup> as having described them.

Much of Langhans' work was done on fresh tissues either teased out or crushed and examined in salt solution, serum or glycerin or in

chromic or acetic acids. He usually made his preparations from fine miliary tubercles of the pleura or peritoneum. He demonstrated the cells, however, in practically every tissue of the body. He felt that they were specific structures and were similar in nature regardless of their tissue source. The question arose in his mind as to whether or not they actually were cells, and because of the action of chromic acid on his fresh preparations, he decided that they were. He found that they varied greatly in shape, size and the number of nuclei. Some were round, some oval, some elongated or sausage shaped, some elliptical, some irregular and some more or less stellate. Some were sharply defined, some had attached mantles of adherent spindle cells and others were less well demarcated. He noted that, in size, they varied from small cells with from two to four nuclei, to large cells measuring from 0.2 to 0.3 mm in diameter and having from thirty to 100 or more nuclei. The nuclei were characteristic, usually round or oval, with sharp outlines and vacuolated centers and generally contained nucleoli. The arrangement of the nuclei was, for the most part, characteristic, it was peripheral, with the long axis of the nucleus at right angles to the cell wall, but this did not hold throughout. Some of the cells had the nuclei grouped in a bipolar arrangement and some had them diffusely distributed throughout the cell. The protoplasm of the giant cell was pale, homogeneous or finely granular, with the center usually clear. Sometimes, the outlines of a fine fibrillar net work could be made out in the protoplasm. In teased preparations the cells became cloudy and cleared when acetic acid was added.

Langhans raised the question whether the cell arose from its own action or was derived from the surrounding tissues. He thought that the giant cells originated from the surrounding cells and that the spindle cells played the principal part. He advanced several arguments for his view. The nuclei were similar to those of the surrounding cells and were situated, as a rule, in the periphery of the cell. Sometimes the surrounding spindle cells were flattened out like plates on the sides of the giant cells and sometimes they extended outward from the giant cells to join with the neighboring cell groups, this observation suggested that the cells were either flowing into the giant cell or being cast off from it. Finally he thought the included fibrillar network resembled the fibrillar arrangements of the surrounding tissues.

He introduced the discussion regarding nuclear division of one cell as opposed to the fusion of several cells to form the giant cell. Although fusion had not been demonstrated in man he considered it possible.

Langhans' description of the giant cell of tuberculosis is classic and complete and the synonymous use of "tubercle giant cell" and "Langhans' giant cell" would be justified if it were not that the description



is just as accurate for any foreign body giant cell as it is for that of tuberculosis. While the term "Langhans' cell" is usually applied only to those cells with peripheral (wandständige) nuclei, Langhans also described the forms with bipolar and diffuse distribution of nuclei, so that it is probably correct to apply the name "Langhans' cell" to any foreign body giant cell.

Further discussion of the tubercle giant cell will be taken up under the head "Occurrence in Tuberculosis."

*The Foreign Body Giant Cell*—The term 'foreign body giant cell' has been applied to a type of multinucleated cell which is identical with Langhans' cell in structure and appearance and which soon appears in the vicinity of any foreign or insoluble substance in the tissues that is too large to be taken up by a single cell.

Mallory<sup>2121</sup> described the foreign body giant cell as follows:

When an endothelial leukocyte finds difficulty in dissolving a substance, as, for instance, lime or certain fat products, it frequently fuses with other endothelial leukocytes to form a multinucleated mass of cytoplasm, commonly termed a foreign body giant cell. If the foreign body is too large for one leukocyte to incorporate (cholesterol crystals, hair, etc.), one or more giant cells are formed which surround it or cluster themselves upon its surface.

The present consensus of opinion appears to be that the only difference between Langhans' giant cells of tuberculosis and foreign body giant cells is one of environment.

The misunderstanding about the nature of the giant cell of tuberculosis and the foreign body giant cell as encountered in other conditions, arose chiefly because of the locations of the nuclei. In tuberculosis, the peripheral, bipolar and horse shoe arrangements are more commonly found, while about inert foreign substances the nuclei tend to be diffusely or centrally placed.

Metschnikoff<sup>266</sup> and later Adam<sup>1</sup> demonstrated that when inert foreign particles were introduced into the body cavities of *Astiopecten* and other lower forms, multinucleated plasmodia were found about them. Ziegler,<sup>88</sup> with some ingenious experiments later to be discussed, obtained foreign body giant cells about glass platelets, and interpreted them as being identical with those found in tuberculosis.

Kockel<sup>195</sup> maintained many years ago that Langhans' cell in tuberculosis was not characteristic but was the accidental presence of a foreign body giant cell in an unusual environment. Kückmann<sup>201</sup> undertook to determine the identity of giant cells as they were encountered in tuberculosis about parasites and foreign substances and in sarcomatous and epithelial tumors. While he believed that the giant cells could arise from several different kinds of mononuclear cells, he concluded that microscopic means were not at hand by which they could

be distinguished Hektoen <sup>148</sup> and recently Maximow <sup>278</sup> stated definitely that Langhans' cell is merely a foreign body giant cell occurring in tuberculosis

On the other hand, Jacobson <sup>168</sup> published an outline for the differential diagnosis of six kinds of giant cells, including those of the tubercle, and Lubarsch <sup>228</sup> said that the picture in tuberculosis is so characteristic that one speaks of the tubercle giant cell to the exclusion of all other forms

Burgess demonstrated that typical Langhans' giant cells could be formed experimentally about the soaps and salts extracted from foci of caseation

*The Osteoclast*—Large multinucleated giant cells are present in practically all conditions in which bone is formed or resorbed. They appear during embryonic development, and are increasing during repair after fractures and in most inflammatory and neoplastic diseases. These cells are the osteoclasts of Kolliker <sup>197</sup> (1873). They measure from 40 to 90 microns long, and from 30 to 40 microns broad. In normal bone, they are found in Howship's lacunas, either singly or in groups, and are active in all conditions in which bony resorption is a part of the process. Kolliker thought that they arose from osteoblasts by repeated nuclear division. In Stohr's Textbook of Histology <sup>36</sup> the statement is made that they do not appear to be due to a fusion of cells and that they have nothing in common, except their large size, with the giant cells of the bone marrow (the megakaryocytes of Howell <sup>164</sup>) but are found along the surface of the bone or in the lacunas. According to Stohr, satisfactory evidence has not been found that osteoclasts are the active cause of bone destruction, they appear to be degenerating cells brought to that pass by the same conditions which lead to bony dissolution. This last statement however is not in accord with the majority of expressed views about osteoclasts.

Kolliker studied them in fresh and fixed preparations. In the fresh state they were indefinite in outline and degenerated quickly. He described them in the long and the membranous bones. Rustizky <sup>311</sup> studied these cells in bony lesions of various kinds including those gathered in a layer against bony margins, those in sarcomas and myelomas, those found in granulomas and those found in the healing of fractures and old calluses, as well as those around hemorrhages and deposits of hyaline fibrin. He concluded that they were giant cells which were not specific for the lesions in which they occurred but were the same throughout. He connected them with bony resorption and said they all contained calcium granules. G. Wegner <sup>369</sup> identified the "plaques à noyau multiples," later known as the "myeloplaxen" of Robin with these giant cells. He found them in the periosteum and

bone marrow of several patients whose cases were associated with resorptive lesions. He thought they came from the proliferation of cells in the vessel walls, and that the nuclei increased through nuclear proliferation of a single cell. As evidence, he pointed out the irregular increase in the number of nuclei, and the constant central grouping of nuclei in the younger cells. Biedichin,<sup>48</sup> quoted by Langhans, thought that osteoclasts were foreign body giant cells, and were formed by the fusion of like cells. Vuchow<sup>350</sup> and Rindfleisch<sup>303</sup> believed that foreign body giant cells and the osteoclasts were the same. Among the more recent writers on this subject, Malloiy<sup>243b</sup> stated that the osteoclast is a foreign body giant cell formed by the fusion of endothelial cells. MacCallum<sup>231</sup> used "great phagocytic cells" of bone and "osteoclasts" synonymously. Ewing apparently did not consider them identical, for he discussed giant cell tumors as osteoclastomas<sup>66d</sup> and as being in a different group from sarcomas containing foreign body giant cells. Maichand<sup>253b</sup> stated that osteoclasts are nothing else but a kind of foreign body giant cell with a special function to perform.

Most modern writers group the Langhans cell of tuberculosis, the foreign body giant cell about inert substances and in miscellaneous granulomas and the osteoclasts together as one type of cell, which forms in response to the stimulus of some foreign substance and which varies morphologically only with local environmental influences.

*The Megakaryocyte*—In addition to the osteoclasts of Kolliker, there is a second type of giant cell present in bone marrow which is known as the "megakaryocyte." It is not a true multinuclear cell but has a large, single multilobulated nucleus which may be crown shaped, irregularly lobulated or polymorphic, and which, according to Bunting,<sup>57</sup> may be made up of several vacuolated nuclei bound together. About the nucleus is a zone of coarsely granular protoplasm, and outside it a relatively clear or finely granular area (Schüdde<sup>324</sup>). Jordan<sup>175</sup> found that the cytoplasm contained mitochondria and a Golgi apparatus. These cells multiply by mitosis (Arnold<sup>8</sup>). They phagocytose red blood corpuscles (Petersol<sup>291</sup>). Wight<sup>384</sup> proved that they give rise to blood platelets through the snaring off of pseudopodia from their protoplasm.

In the German literature prior to 1890, these cells were generally discussed collectively under the name "Knochen Riesenzellen." Maichand<sup>253b</sup> credited M. Heidenham<sup>116</sup> (quoted by Schmaus and Albrecht,<sup>17</sup> 1892) with the separation of the giant cells of the bone marrow into two groups: the "Knochenmarkzellen," or "Riesenkernzellen" and the "Riesenzellen of Kolliker," or osteoclasts. Two years earlier, Howell<sup>164</sup> had differentiated these cells and separated them into the two classes. Howell appears to have been the first to apply the term "megacaryocyte." As Maichand pointed out, they have nothing to do with each other.

With modern technical methods, megakaryocytes are readily excluded from the group of foreign body giant cells, and need not be discussed further.

*The Giant Cells of the Muscles*—Two kinds of giant cells have been described as occurring in striped muscle—the multinucleated forms of the rhabdomyosarcoma which are actually atypical muscle cells (Ribbert<sup>301</sup>), and about the nature of which there is no doubt, and the repair clubs of striped muscles, which have frequently been mistaken for foreign body cells. Virchow<sup>171</sup> mentioned the resemblance of the latter type to myeloplaxes, and Maichand<sup>2531</sup> included them among his sources of foreign body giant cells. Lejars<sup>216</sup> described tuberculosis of muscle with the formation of Langhans' cells from the striped fibers. Mallory<sup>242c</sup> explained the various appearances in injured striped muscle which simulated giant cells as follows:

When the whole muscle fiber is killed, it is not regenerated. When only a part of one of the fibers is destroyed, active regeneration of the part which has not undergone necrosis takes place from the part which remains uninjured. The intact nuclei undergo rapid direct division and each forms several dozen separate nuclei. The division of the nuclei may take place at the periphery of the cell, or in the center of its own axis. The new nuclei migrate to the periphery and the injured end of the muscle fiber. The partially dead muscle cell may be removed by polymorphonuclear leukocytes, and at other times endothelial leukocytes attack it and dissolve it, working from without inward. Mitoses in these endothelial leukocytes are not infrequent. Occasionally multinucleated cells result. More often they fuse to form foreign body giant cells. Sometimes the two processes go on at once, and render the picture difficult to interpret.

While muscle repair clubs may resemble foreign body giant cells, it is doubtful if they can take part in their formation in any capacity other than that of a foreign body which attracts them.

*The Giant Cells of Nerve Tissues*—True foreign body giant cells, as well as other structures closely resembling them, may occur in nerve tissues. Completely degenerated ganglion cells without nuclei may be closely surrounded (neuronophagia) by phagocytes in such a way that the resemblance to giant cells with peripherally situated nuclei is simulated. Degenerated and inflamed nerves may also have their sheaths infiltrated with phagocytes so that they present a somewhat confusing picture. Indeed, true giant cells may be found in nerve trunks in leprosy and other granulomas. Areas of ischemic softening, hemorrhagic extravasations and other injury in the brain may contain many phagocytes which may be single or multinucleated. The question has been raised as to whether the phagocytes in these areas are of mesoblastic or of glial origin. Alzheimer<sup>2</sup> divided glial cells into four groups, the second of which was made up of ameboid phagocytic forms which were active in phagocytosing injured brain substance. Giant cells are con-

stantly present in tuberculosis of the brain and in gummas, and it is accepted that these are ordinary foreign body giant cells. It seems therefore unnecessary to interpret the phagocytes of hemorrhagic areas in the brain as having a special origin from glial cells. According to Buzzard and Greenfield,<sup>61</sup> the question is not settled.

*Syncytial Giant Cells*—In his series of articles on endothelial reactions, N. C. Foot<sup>101-105</sup> frequently makes references to the "large syncytia" of the tubercle. As one definition of syncytium is a group of cells without separating walls, this application of the term is, no doubt, correct. However, it has the disadvantage of using a name which was formerly applied to the multinucleated giant cells arising from the syncytial layer of chorion called the "syncytial" or "placental," giant cells.

Placental giant cells are not related in any way to the foreign body giant cells, though they resemble them. They are tangential sections through the buds of syncytial cells on the villi of the developing placenta (Williams,<sup>380</sup> Cullen<sup>78</sup>). They were reported as occurring in the capillaries of the lung by Schmoil<sup>122</sup> in 1893, who considered their presence in that location as a part of the pathology of eclampsia. Luesden,<sup>231</sup> in 1895, also studied the pathologic changes of eclampsia and found the giant cells, but stated that they occurred in normal pregnancies as well, and had nothing to do with eclampsia. Aschoff<sup>10</sup> reported multinucleated syncytial cells embedded in the wall of the uterus in a specimen removed during cesarian section and considered them to be placental giant cells squeezed off by uterine contraction. They are now generally recognized as a constant observation in pregnancy. The question of the source of these cells was for a long time in doubt. McCallum<sup>2,3c</sup> pointed out that it has always been admitted that the Langhans layer originates from fetal ectoderm, but that the syncytial layer has been variously attributed to maternal epithelium, to maternal endothelium and to fetal ectoderm. Marchand<sup>51</sup> maintained that both layers came from fetal ectoderm and Schlagenhaufen<sup>16</sup> described these cells in chorion epithelioma of the testis which completely ruled out the maternal sources and left fetal ectoderm as the only possibility.

Other epithelial syncytia are often mentioned interchangeably with giant cells. Aschoff described large masses of multinucleated syncytia in the liver in lobular hypertrophy and repair of lobules of the liver and in cirrhosis and adenoma of the liver. I have recently seen two such cases and agree with Aschoff that these masses while true syncytia in liver cells, are in no way related to foreign body giant cells. Such masses commonly contain numerous large mitotic figures. Rowen and Mallory<sup>310</sup> reported a case of carcinoma of the liver in which the type cells were large syncytial cells.

These cells should not be confused with foreign body giant cells, to which they do not have any relation

*True Tumor Giant Cells*—Almost any rapidly growing tumor is likely to present multinucleate tumor cells. The sarcoma group is particularly apt to present such forms, and often contains ordinary foreign body giant cells as well. The true multinucleated tumor cells tend to differentiate like the mononuclear cells of the tissues from which they originate, and are characterized by their somewhat larger size, the number of their nuclei, the presence of mitoses, which may be atypical and of "giant" size, and the tendencies to contain hyperchromatic nuclear structures and multiple nucleoli. Further, they degenerate like the cells from which they come, and metastasize with other tumor cells. Save for the hyaline inclusions which are seen in some epithelial tumor cells and for fat and granular debris, they rarely contain phagocytosed particles. As characteristics which differentiate them from foreign body giant cells may be mentioned their shape, which usually conforms in a general way with that of their fellows, the fewer nuclei usually not more than six or eight, and the striking irregularities of their nuclei with reference to chromatin content and staining qualities. The foreign body cells usually are round or globular, tend to retract from the surrounding cells on fixation, have large numbers of typical nuclei, and often contain phagocytosed granules, particles of chromatin, entire cells and cellular debris.

A detailed discussion of the various types of tumor cells will be taken up in a later section.

*Summary on Varieties of Giant Cells*—It is probable that the giant cells of inflammatory lesions including tuberculosis and other chronic granulomas, those about foreign bodies and those in bones known as osteoclasts, are variations of the so-called foreign body giant cell and are similar in origin and function. They will form the nucleus of the remainder of this discussion.

Megakaryocytes, muscle giant cells, syncytial giant cells and true tumor giant cells are specialized cells of distinct origins and separate functions, and are hereafter excluded from the general discussion. The various tumor cells will be considered as a part of the discussion of the occurrence of giant cells in tumors.

#### CELLS FROM WHICH GIANT CELLS HAVE BEEN REPORTED TO DEVELOP

In the earlier literature the greatest confusion existed in regard to the types of cells from which giant cells could develop. Virchow<sup>372</sup> at first thought that they came exclusively from the cells of connective tissue, but later admitted the possibility of their origin from epithelium, from endothelium and under certain conditions, from the cells of the

muscles and the nerves Marchand's idea was that, since any large protoplasmic mass with more than one nucleus was classed as a giant cell, there must be many kinds. He believed that they differed greatly in significance, and that they could originate from various tissues, such as epithelial cells, muscle cells, connective tissue cells, fat cells, leukocytes and lining, or pavement, cells of the serous cavities and blood and lymph vessels. Few authors adhered entirely to a single source, and Arnold, who wrote four papers in support of the development from tubular epithelium, considered that they arose from endothelium<sup>6</sup> in the lymph nodes.

Gradually the theories of origin from fixed endothelium and from epithelium, aside from the alveolar epithelium, have lost ground. Giant forms of the cells of muscle and nerve have been explained on a different basis, and megakaryocytes and placental syncytia have been recognized as unassociated structures, and so have been automatically removed from the possibilities. The arguments now rest on modifications of the Baumgarten<sup>29</sup> theory of origin from fixed connective tissue and proliferated endothelial elements and the theories of origin from wandering cells (Ziegler<sup>38</sup> and Bonnel<sup>43 44</sup>). In an attempt to present an idea of the sources of giant cells described in the literature I have classified the views under several headings.

*Origin of Giant Cells from Fixed Connective Tissues*—Baumgarten,<sup>27-30</sup> E. Wegner,<sup>35</sup> Lubimow,<sup>270</sup> Brissaud and Toupe,<sup>50</sup> Billroth,<sup>31</sup> Kostenitsch and Wolkow<sup>200</sup> Stiaus<sup>378</sup> and Klebs<sup>188 189</sup> were among the earlier writers who traced the formation of the tubercle to the cells of fixed connective tissue, and the tubercle giant cells, in turn, from the epithelioid cells. Some as will later be shown, explained them on the basis of nuclear division, some by fusion of the involved cells, and some by degeneration and compression in such a way that the cell boundaries were lost. Rindfleisch<sup>304</sup> studied the process of organization and encapsulation, and reported that the cells extending from the surrounding cells to the giant cells produced fibrils of true connective tissue. Falk,<sup>98</sup> in 1895, emphasized the fact that nearly all observers had given up the idea of giant cells coming from exudative cells, and had returned to the old idea of Virchow that giant cells come from the cells of fixed connective tissue. He himself shared in Baumgarten's idea that the tubercle came from fixed connective tissue which became infiltrated with wandering cells.

*Origin of Giant Cells from Tubular Epithelium*—A fairly large number of pathologists were misled by the resemblance between giant cells with peripheral nuclei and hollow tubular structures such as epithelial lined ducts and endothelial lined blood and lymph vessels, into postulating that giant cells were derived from such structures. Arnold, in several papers on the histogenesis of the tubercle traced giant cells to epithelial ducts in every organ in which such structures occurred. In lymph nodes, endothelium, he believed tended to undergo cornification into epithelioid cells and subsequently to change into giant cells. In

1880, he compared experimental tuberculosis of the liver in animals with his material obtained at autopsy, and concluded that giant cells came from bile ducts. He pointed out that giant cells and bile ducts were always found together in tuberculosis of the liver, and he believed that he was able to recognize every step in the transformation. He argued that the peripheral arrangement of nuclei, which had always been difficult to explain, became clear at once when tubular epithelial structures in tuberculous lesions were studied. In subsequent papers, Arnold<sup>4, 5</sup> reiterated the statement that the origin of giant cells was from bile ducts, and also described their origin from epithelium of the seminiferous tubules in tuberculosis of the testis, from tubular epithelium in the kidney and the possibility of their origin from any small epithelial duct or hollow epithelial canal in the body. While he discussed the origin of giant cells from sinus epithelioid cells in lymph nodes and from alveolar epithelium in pulmonary tuberculosis, Arnold most enthusiastically advocated their origin from tubular structures. Waldstein<sup>6</sup> described "plates" of giant cells in the seminiferous tubules in tuberculosis of the testis. He found these cells fusing directly with the lining epithelium, and believed that the giant cells were epithelial outgrowths. Tizzoni and Gaule<sup>11</sup> described the same giant cell pictures in the testis, but raised the question of their accidental occurrence in these sites. They did not deny that the cells came from the epithelium but thought it more likely that they originated from the associated lymph channels. Boist,<sup>15</sup> Paltauf,<sup>27</sup> Buch-Hirschfeld<sup>17</sup> and many others expressed themselves in favor of the origin of giant cells from tubular epithelium.

*Origin of Giant Cells from Surface and Glandular Epithelium* — Aside from epithelial tumors, the origin of giant cells from surface epithelium has not been frequently reported. Askanazy<sup>16</sup> traced them from the deeper layers of the skin after freezing the ears of rabbits with a mixture containing ether and Weigert described "epithelial" giant cells in the margins of smallpox pustules. Kiuckmann<sup>201</sup> who made an extensive study of giant cells in experimental tuberculosis, in tuberculosis found at autopsy, and in tumors, thought that, while they usually arose from endothelium or fixed connective tissue they could come from the fusion of displaced squeezed or compressed degenerated epithelium. Krause<sup>202</sup> also studied the giant cells in epitheliomas and thought that those in the granulations about the tumor columns came from tumor epithelium. Boist<sup>17</sup> repeatedly asserted the epithelial nature of epithelial tumor giant cells. Kiuckmann included his series of tumors in dermoid cysts and sebaceous adenomas and found giant cells which he attributed to epithelium. Zielonko<sup>200</sup> reported them in chalazions and in the adenomas of the meibomian glands. I have seen them several times in the small xanthomas of the eyelids. Here the resemblance between the sebaceous glands filled with vacuolated sebaceous cells and the nests



of fat filled phagocytes, so-called "compound granule cells," is striking. It is easy to be mistaken, but I believe that the giant cells come from the compound granular cells.

Emanuel<sup>90</sup> believed that giant cells in the ovary could originate from lutein cells. It might be noted also that compound granular cells are common in ovarian inflammation, and that the resemblance between them and luteal cells is close enough to lead to error.

*Origin of Giant Cells from Alveolar Epithelium*—In view of the lack of unity of opinion concerning the phagocytes of the lung and the application of the term alveolar epithelium to them, it seems best to consider them in a separate paragraph.

Formerly, it was pretty generally accepted that alveolar epithelium desquamated readily and took an active part in all the exudative lesions of the lung. The desquamated alveolar cell was described, and still is in many textbooks, as one of the first cells found in the exudate of pneumonia, and as the active phagocyte in the various dust diseases, the pigment phagocyte of chronic passive congestion, often called the "heiz fehler zellen," and so on. There is no doubt that a phagocytic cell is active in all the processes mentioned, as well as in many other lesions, including the formation of miliary tubercles and of giant cells, but there appears to be a preponderance of evidence that the phagocyte is not an epithelial cell. With the conception of the epithelial origin of this cell, however, it was to be expected that tubercles and giant cells should be traced to "alveolar epithelium." Conspicuous among the group who described tubercles and giant cells as originating from the epithelium of the lung were Arnold,<sup>7</sup> Buhl,<sup>56</sup> Klein,<sup>100</sup> Friedlander,<sup>117</sup> Betzke,<sup>122</sup> and Heixheimer.<sup>176</sup>

Mallory,<sup>29</sup> in 1898, in his studies on typhoid fever, described the origin of the mononuclear phagocytes of the body from the walls of proliferating capillaries. The cells under the stimulus of the typhoid bacillus or its toxins underwent rapid proliferation and swelling, frequently showed numerous mitoses, and then wandered out into the surrounding tissues or were thrown off into the lumina of vessels. These cells were phagocytic and were called "endothelial leukocytes." While working in Mallory's laboratory from 1908 to 1910 I learned his views, namely, that the endothelial cell was the active cell of the tubercle, and was the source of the phagocytes of the tissues and of the lung alveoli. The cells took up granules of pigment, tubercle bacilli and all sorts of foreign particles and were thought to fuse to form giant cells. Mallory advocated the endothelial origin of the lung phagocyte strongly, and denied the phagocytic action of the alveolar epithelial cell.

In 1912 while associated with Klotz,<sup>102-109</sup> I made a series of studies on the development of pulmonary anthracosis in part experimental and

in part based on the anthracotic lungs encountered at autopsy in the Pittsburgh district. In the experimental work, I used india ink and finely ground lamp black, which was blown into the animals' larger air passages. I followed tubercle formation and giant cell development from wandering phagocytic cells, which were identified by their having taken up both the granules of pigment and the tubercle bacilli. The results obtained experimentally were supported by the studies on lungs removed at autopsy from human patients. In the study of the latter, a special stain was used which was not differential for the epithelium of the lung, but which made it possible to study the epithelium *in situ*. I found many alveoli filled with alveolar phagocytes in which the epithelial lining cells were intact and free from phagocytosed particles. I found alveoli in all the stages of pneumonia with the air spaces full of so-called alveolar epithelial phagocytes and with the lining cells still attached to the walls. Not once did I find pigment or other phagocytosed material in attached alveolar epithelium or in groups of definite lung epithelium which had desquamated in strips. I am convinced that the alveolar phagocyte is not of epithelial origin, but whether the cell is derived, according to Mallory's idea from capillary endothelium, or according to McJunkin,<sup>25</sup> from the mononuclear cells of the blood, or as stated by Gardner and Smith<sup>117</sup> from an interstitial lung cell—I am uncertain. I did not have sufficient evidence at the time to conclude, as I did that it was a wandering endothelial cell of capillary origin.

A majority of present day authors are agreed that the giant cells of the lung come from the alveolar phagocytes, so that some review of the subject is necessary. For a detailed review of this phase of the question, the reader is referred to the comprehensive article by Foot.<sup>107</sup> The recent active interest in the origin of the alveolar phagocyte is closely associated with the advent of vital staining. Sewell<sup>370</sup> in 1918, studied vitally stained lungs, and concluded that the phagocytes were epithelial. His articles were answered by Foot<sup>102, 103</sup> and by Peimar,<sup>253, 255</sup> using various methods of vital staining, both authors supported the endothelial origin. Mallory and Medlar,<sup>213</sup> reporting on the pathology of measles, demonstrated the presence of lung phagocytes associated with marked capillary endothelial proliferation in the lung. Their work was supported by Blake and Trask<sup>76</sup> in a study of experimental measles. Sewell, Aschoff,<sup>13</sup> Kiyono,<sup>185, 186</sup> and Gross,<sup>127</sup> actively maintained the epithelial nature, while Peimar, Klotz,<sup>192, 193</sup> and until recently Foot<sup>107</sup> stood out for the endothelial nature of the phagocytes. Foot still denies their origin from epithelium, but admits the possibility of their derivation from blood monocytes and interstitial cells. Gardner, who formerly believed in the endothelial origin of the phagocytes, studied paraffin sections of lungs vitally stained with neutral red and concluded that the

phagocytes came neither from endothelial nor from epithelial cells, but from interstitial septal cells of the alveolar walls, and that they belonged, therefore, to the group of connective tissue phagocytes. Fried<sup>112</sup> begged the question by calling the alveolar epithelium a special kind of mesothelium which is able to desquamate and act in a phagocytic capacity. It may be noted, by way of comment, that any cell, whatever its nature, in passing from a capillary to the alveolus, must occupy the position of a septal cell during a part of the migration, and that the stain used by Gardner also stains the mononuclear leukocytes of the blood. While there is little evidence, under normal conditions, that the capillary endothelium of the lung is a source of mononuclear leukocytes, under inflamed conditions, the appearance is different, and the observations of Malloiy in typhoid and of Malloiy, Medlar, Blake and Task in measles, are hard to explain in any other way save that the capillaries of the lung may, at times, become an accessory source of phagocytes.

The formation of giant cells from alveolar phagocytes is generally conceded by modern observers.

*Origin of Giant Cells from Serosal Mesothelium*—The participation of the mesothelial or serosal epithelium in the formation of the tubercle giant cells and in the formation of foreign body giant cells has been noted by many workers. Marchand,<sup>250</sup> from his earlier experiments with bits of sponge placed in the peritoneal cavity, described the proliferation of the mesothelial cells and their subsequent extension into the meshes of the sponge with the formation of giant cells. Heizog<sup>161</sup> recently repeated Marchand's work, and reiterated his statement. Metschnikoff<sup>216</sup> held a similar opinion. Karsner and Swanbeck<sup>181</sup> reported the formation of giant cells in the pleura. Koster<sup>201</sup> studied the histogenesis of tuberculosis of the knee joint and said that the giant cells developed from the serosal lining cells and from the endothelium of the lymph channels. Rindfleisch<sup>203</sup> discussed the origin of giant cells from serosal endothelium in experimental tuberculosis of the omentum, by which he apparently meant mesothelium. Mesothelium is closely related to vascular endothelium in activity and appearance, but that it gives rise to wandering phagocytes is not universally conceded.

*Origin of Giant Cells from Fixed Endothelium*—Beginning with von Schuppel<sup>226</sup> a great many observers have attributed the origin of giant cells to endothelial structures. Their theories fall into two classes: those which explain the presence of giant cells directly through changes in fixed endothelium, and those which have to do with endothelium as the source of wandering cells which later become transformed into giant cells.

For convenience of discussion the theory of their origin from blood vascular endothelium and that of their origin from the lymph vascular

endothelium will be taken up, in turn, in the succeeding paragraphs, while the theory of their origin from wandering cells will be reviewed in the section on "exudative cells."

Ziegler credited Schuppel with being the first to advance the theory of the blood vascular origin of giant cells. According to Schuppel, the vessels in a tuberculous area become filled with a nonnucleated protoplasmic mass, the endothelium of the walls then proliferates and the appearance of a giant cell with peripheral nuclei develops, sometimes the vascular endothelium proliferates concentrically to such an extent that a complete cellular occlusion of the vessel occurs, and a giant cell with centrally placed nuclei is found. In a later article in which von Schuppel<sup>25</sup> identified "pearlsucht" in cattle with tuberculosis, he enlarged somewhat on his earlier views. He argued that a tubercle often starts within the lumen of a capillary where there are no lymphatics and that since every tubercle has a giant cell as its beginning, this cell must be of blood vessel origin. Later the vessel becomes closed and appears as a giant cell, the other surrounding tissues caseate, and only the giant cell remains to mark the site of the vessel. He felt certain that giant cells came only from blood vessels, and that the appearance was due to hyaline thrombi invaded by Cornil, Besançon and Giffon.<sup>71</sup> Reached similar conclusions from their studies of meningeal tuberculosis. Kockel<sup>197</sup> followed the formation of giant cells in the portal veins and concluded that they were thrombosed vessels and that the appearance was due to hyaline thrombi invaded by endothelium which extended in from the vessel walls. Brodowski,<sup>72</sup> Babes<sup>19</sup> and recently Wurm<sup>66</sup> concluded that the giant cells of tuberculosis are anomalous outgrowths of endothelium from vessel walls. Brosch<sup>71</sup> thought that giant cells could arise from capillary extensions which he called angioplasts, or from connective tissue cells which could take on endothelial characteristics and change to giant cells. He said that by proliferation of the endothelium of degenerated vessels, and in no other way, could giant cells with double rows of peripheral nuclei be explained. Rindfleisch (quoted by Langhans<sup>211</sup>), Deichle,<sup>81</sup> Colberg<sup>70</sup> and Manz<sup>218</sup> all supported the theory of the origin of giant cells from blood vessels, in some instances. Friederich and Noesske<sup>115</sup> observed the formation of giant cells in the vessels of the kidney following the intravenous injection of tubercle bacilli. Miller<sup>119</sup> and Bowman Evans and Winternitz<sup>51</sup> studied the formation of tubercles from Kupffer's cells in the liver sinusoids. Foot<sup>105</sup> traced them in the meningeal vessels, and Gardner<sup>21</sup> Medlar<sup>260</sup> and Haythorn<sup>143</sup> found them in the vessels of the lungs and the spleen in experimentally produced tuberculosis. In such situations the sources of giant cells are practically limited to endothelium and blood mononuclears.

The theory of the origin of giant cells from the endothelium of the lymph channels was held by Vichow, at first. Later, he accepted several other possibilities. Koster<sup>201</sup> and Heining<sup>157</sup> interpreted giant cells as cross sections of lymph channels with proliferated endothelial walls, and Cacciola<sup>65</sup> held a similar opinion, with the added conception of a thrombotic occlusion of the channel to explain the marginal situation of the nuclei. Tizzoni and Gaule<sup>345</sup> accepted the view of Heining but their descriptions and plates clearly show that the structures which they described as lymph channels were the retraction spaces of the ordinary miliary tubercle as we understand it today. They interpreted the clear space and the bits of caseous material so often seen in the center of a miliary tubercle as the lumen of the lymph channel. The partially or completely formed giant cells they took to be endothelial proliferations of the channel wall extending into the lumen. The roset of epithelioid, endothelioid or endothelial cells, they thought represented the proliferated channel wall itself. Their observations on similar appearances in the testis have already been mentioned.

Klebs<sup>188</sup> was one of the earlier experimenters to follow the formation of tubercles and giant cells in lymph nodes. He found that the early tubercles began in the sinuses and developed from the cells of the endothelial lining. These at first became epithelioid cells and later formed giant cells. Manasse<sup>245, 246</sup> reported similar observations. Ribbert<sup>300</sup> and Lubimow<sup>230</sup> favored the theory of the formation of tubercles and giant cells from the endothelial cells of the centers of the germ follicles of the lymph nodes.

Jacobson<sup>168</sup> reviewed all the possibilities of the formation of giant cells from vessels lined by endothelium, and concluded that giant cells might be cross sections of lymph vessels but that it is unlikely, since they are constantly found in granulation tissues in which preformed lymph spaces do not exist, and that they are not thrombosed blood vessels, because thrombi in even the latest stages of degeneration contain occasional blood cells or fibrin which serve to identify them.

The various theories which assigned the origin of giant cells to cross sections of vessels were quickly overthrown with the general adoption of serial sections by which it was found that the giant cells can be followed through comparatively few sections, while vascular structures often extend throughout an entire paraffin block.

*Origin of Giant Cells from Exudative Cells*.—In 1875 Ziegler<sup>385</sup> issued a monograph on the formation of giant cells from exudative white cells. He implanted small glass plates cemented together in pairs in animal tissues. At first he placed the plates in the abdominal cavities of guinea-pigs later in the pleural and pericardial cavities and finally in the intermuscular and subcutaneous tissues. In the latter locations he

obtained satisfactory preparations and conducted seventy odd experiments. He removed the plates from day to day, and was able to follow the changes in the cells between them. He did not actually produce tubercles in this way, but did obtain all the cells ordinarily encountered in miliaary tubercles including typical giant cells. He concluded that tubercles could be formed from exudative cells alone and that giant cells were formed especially from mononuclear cells, probably from both lymphocytes and large mononuclears. He did not assert that all tubercles and all giant cells were necessarily formed in this way, but he did think that it was possible. Ziegler's views met with active opposition on all sides, particularly from the authors who believed only in fixed tissue as the origin of the giant cells.

Marchand,<sup>270</sup> in 1888, made extensive experimental studies of foreign body giant cells by placing pieces of sponge, hardened tissues of the lung, liver, blotting paper and other substances in the peritoneal cavities of guinea-pigs. He found the spaces of the sponges and the air spaces of the hardened tissue of the lung filled with exudative cells and granulations. Many of the preparations contained large foreign body giant cells. Marchand concluded that there were different kinds of giant cells and that they were probably not all formed in the same way. He thought the large multinucleated cells were formed by fusion. He found many mitoses in the granulating areas adjoining, but none in the giant cells themselves.

Borrel<sup>43-44</sup> in 1893, injected cultures of tubercle bacilli into the circulation and stated definitely that giant cells were fused masses of mononuclear leukocytes. Yersin<sup>386</sup> supported Borrel's view, which is now widely accepted.

The discussion as to the origin of the mononuclear leukocyte itself is still far from settled. Several relatively complete reviews on the nature of the large mononuclear leukocyte were published recently, the reader is referred to them for detailed information. Foot<sup>106</sup>, Sabin,<sup>312</sup> Maximow,<sup>279</sup> Jaffé<sup>172</sup> and Sacks<sup>314</sup>. A brief summary of the views on the origin of the mononuclear leukocytes from which giant cells may be formed follows.

Some have held that mononuclear leukocytes are derived from vascular endothelium. Mallory,<sup>239</sup> in 1898, discussing the pathologic changes of typhoid fever pointed out the rapid proliferation of the capillary endothelium in that disease. He interpreted this proliferation as leading not only to the closure of some of the capillaries, indirectly causing focal areas of necrosis and to ulceration of the tissues supplied but also to the formation by the capillary walls of endothelial cells which become wandering mononuclear phagocytes. Subsequently, Mallory<sup>242a</sup> interpreted this form of capillary proliferation as the source of all the mono-

nuclear leukocytes of the blood and tissues, including such variations as heart failure cells, compound granular cells, the cell essential in forming the miliary tubercle and foreign body giant cells. These cells, which he called endothelial leukocytes, he believed, fused to form giant cells. Mallory had many followers. McJunkin,<sup>235</sup> Foot, Permar,<sup>285</sup> Medlar,<sup>261</sup> Haythorn<sup>179</sup> and others. Capillary activities similar to those in typhoid fever were reported observed in measles by Mallory and Medlar<sup>243</sup> and by Blake and Trask,<sup>78</sup> in typhus by Wolbach, Todd and Palfrey,<sup>183</sup> in Rocky Mountain fever by Wolbach,<sup>382</sup> and in tularemia by Permar and Wiel.<sup>287</sup> Foot<sup>101</sup> and McJunkin subsequently modified their views somewhat, questioning the origin of nongranular monocytes exclusively from vascular endothelium. Sabin, Doan, Cunningham and others considered that some of the mononuclear leukocytes are formed by proliferation of capillary endothelium, and that others belong to the myelogenic group. F. A. Evans<sup>93</sup> accepted their interpretation.

Others have held that the mononuclear leukocytes take their origin from "reticulo-endothelium." Some of the early pathologists used the expression "endothelium of the reticulum of the germ centers" in discussing tuberculosis. The work of Downey,<sup>83</sup> Aschoff<sup>1</sup> and Kiyono<sup>185</sup> established the term in its present sense. Reticulo-endothelial cells are defined as endothelium resting on a special reticulum, which are phagocytic in situ and take up vital stains readily. The reticulo-endothelial system includes the endothelial cells lining the sinusoids of the liver (Kupffer's cells) and similar cells of the spleen, bone marrow and lymph nodes. Aschoff, Kiyono and others, working with vital stains, attributed the origin of part of the mononuclear leukocytes of the blood and tissues to reticulo-endothelium. Mallory and Parker<sup>244</sup> showed recently by a long series of microchemical reactions that the reticulum supposed to be formed by endothelium is really collagen, and is derived from connective tissue cells. They stated that endothelial cells do not form reticulum. Since all the endothelium of the body rests on connective tissue, and a group of cells capable of forming a special reticular substance does not exist, the use of the term reticulo-endothelium to denote a specific group of endothelial cells does not seem to be sufficiently differential to be justified.

Other authors have supported a lymphocytic origin of mononuclear leukocytes. After the early work of Ziegler, numerous authors concluded that lymphocytes change into large mononuclear wandering cells and later into epithelioid and giant cells. Recently, Maximow<sup>258</sup> and Bloom<sup>42</sup> published the results of studies of tissue cultures, they concluded that lymphocytes change into large mononuclear wandering cells which Maximow called "polyblasts." In his work on the development of tubercles in vitro Maximow reported that "polyblasts" arise

partly from local "resting wandering cells" of the tissues (such as clasmatoocytes and histiocytes) through rounding off and mobilization, and partly from lymphocytes nongranulated white blood corpuscles and monocytes which may migrate from the vessels or which may have been previously present in the tissues. The polyblasts hypertrophy and join the local histiocytes, become ameboid phagocytic cells and change into epithelioid cells, which may later fuse to form giant cells. According to him, the vascular endothelium does not take part in the process. He concluded with the statement that lymphocytes are slower but nevertheless, become transformed into epithelioid cells.

Here the views of Mallory and Maximow are directly opposed on two important points. Mallory holding that the large mononuclear cells which become epithelioid cells come from endothelium and that lymphocytes never become phagocytes, Maximow that vascular endothelium does not play a part in the formation of mononuclear cells and that lymphocytes change into phagocytes and epithelioid cells.

Perhaps the stains used have something to do with the disagreement. Maximow used hematoxylin and azure II. Mallory fixed his material in Zenker's solution and stained with eosin-methylene blue or phloxin-methylene blue. The latter stain is highly differential for the cells of the lymphocytic series and for mononuclear cells in tissues, and while lymphocytes and plasma cells stain alike. I have not yet seen any cell that still retained the violet tinge of the lymphocyte-plasma cell series acting as a phagocyte.

*Wandering Phagocytes of the Tissues* — Perhaps no other cell in the body has given rise to so much discussion as the wandering large mononuclear phagocyte of the tissues. Views differ on its nature and origin and as to whether it is a local product having a specific function, or merely appears temporarily from the general circulation in response to a stimulus. It seems best to review briefly the conclusions concerning this cell, even at the risk of repeating part of the data covered by the paragraph on exudative cells, for this cell whatever it actually is, plays an important rôle in the formation of giant cells. According to Mallory<sup>2421</sup> it is of vascular endothelial origin, and is identical with the endothelial leukocyte of the general circulation. According to Sabin<sup>212</sup> it may be either of two cells one of which comes from endothelium and the other from the myelocytic series. Aschoff<sup>11</sup> classified it as a tissue histiocyte of reticulo-endothelial origin. Maximow<sup>277</sup> called it the "resting wandering cell" or "polyblast" and derived it primarily from the mesoderm but also from wandering lymphocytes. Ranvier<sup>296</sup> called it the clasmatoocyte. Simpson<sup>331</sup> called it a macrophage and by the use of vital stains separated the macrophages from lymphocytes. McJunkin<sup>237</sup> by the use of the benzidine reaction and by staining with



neutral red, identified three types which he called monocytes, lymph-endotheliocytes and hemendotheliocytes, the lymphendotheliocyte being the one which he considered the source of the epithelioid cells, but which is not related to the lymphocytes. These cells appear to be the same as those called pythol cells by Goldmann,<sup>12</sup> macrophages by Metschnikoff<sup>266</sup> and Evans,<sup>94</sup> monocytes by Pappenheim,<sup>251</sup> adventitial cells by Marchand,<sup>255</sup> and so on. Kaisner,<sup>178</sup> after carefully reviewing the question in his recent textbook attempted to be impartial adopting two new terms namely "endotheliocytes" and "endothelial phagocytes."

Whatever the exact nature of this cell may be, and whether it represents a single specific cell or a group of closely allied cells it is this cell or cell group which is most intimately concerned in the formation of the Langhans or foreign body giant cells.

#### THEORIES OF THE FORMATION OF GIANT CELLS

In discussing the theories of the formation of giant cells, the cell in question is the foreign body giant cell, including the Langhans cell of tuberculosis and the osteoclast. Langhans, in his original article, said that there were two ways in which these cells might be accounted for (1) by division of the nuclei without division of the cell, and (2) by the fusion of several cells to form a single large cell. Each theory has had numerous adherents and the question of the correctness of either to the entire exclusion of the other has not yet been settled. It is known that nuclei may divide without the complete division of the cell, in many instances, and it is conceded that this is the usual process of formation of the multinucleated muscle repair cells, megakaryocytes, epithelial syncytia and tumor cells. It has been proved also, that cells of the types from which giant cells are formed may fuse to form large single cells in cultures. It is likely that either or both of these processes may take place in the living animal, depending on external influences and environmental conditions. The time required for the formation of giant cells has usually been given as varying from about eight to fourteen days in experimental animals, and even less in tissue cultures. Marchand obtained his most beautiful pictures in about thirty-five days.

*Nuclear Proliferation*—A great many observers have accepted the theory of nuclear division to account for multinucleated giant cells in spite of the fact that mitotic figures in these cells are of extremely rare occurrence. Kompecher<sup>200</sup> made an extensive investigation of cellular division, and applied his researches in part to osteoclasts. He said that the nuclei could divide by mitosis or by amitosis including direct division, and by direct and indirect fragmentation. Mitosis might be single, double or multiple leading to two, four or many nuclei respectively, and followed a proliferative stimulus in a healthy growing cell. Amitosis could

take place by direct division, which was the simple constriction of the nucleus and its division into two equal parts, or by direct fragmentation, in which bits of the nucleus were snared off in a manner resembling budding, or, finally, by indirect fragmentation, in which the particles of chromatin became diffused throughout the cell and rearranged into two or more nuclei. Amitosis took place in poorly nourished or degenerated cells, though it was possible for both mitosis and amitosis to go on simultaneously in the same cell. Mitosis meant a progressive lesion, amitosis indicated a retrogressive one. He emphasized the theory in embracing Weigert's conception of the formation of giant cells in tuberculosis. Weigert believed that when tubercle bacilli became localized in an area, they were taken up by cells which then underwent rapid proliferation by mitotic division. The tubercle bacilli also multiplied and produced a toxic effect on the cells so that when mitosis began in the usual way the vitality of the cell was so lowered that division was limited to the nuclei, and complete division of the cell could not follow. Later, the central portion of the cell died and the nuclei continued to live and multiply in a zone of living protoplasm in the periphery. Baumgarten,<sup>30, 30a</sup> who was an early advocate of nuclear division taught that giant cells were formed by multipolar division of fixed cells. He did not believe that fusion could occur as a part of an active process which led to multiplication of all the cells in the area. Later, he accepted Weigert's explanation and since both were emphatic in their stands that the giant cell was the result of a combination of multiplication and degeneration of fixed tissues the theory has become widely known as the Baumgarten-Weigert theory.

The advocates of mitotic division of nuclei have been comparatively few. Cornil,<sup>74</sup> Manasse,<sup>210</sup> Goldmann,<sup>122</sup> and Foot,<sup>104</sup> described mitotic figures. Hammerl<sup>135</sup> saw one figure, Justi observed two instances of mitosis but was a strong believer in direct division. Malloiy in a personal statement to me, said that he had not found a mitotic figure in a giant cell which could not be explained on the basis of a cell that had been phagocytosed during mitosis. I have been shown two instances of mitosis in giant cells one by Gardner and the other by Cohen. I think that Malloiy's explanation could be applied in both instances but it is difficult to establish this point. Advocates of direct division have included Koch,<sup>194</sup> Duval and White,<sup>88</sup> Lubimow,<sup>230</sup> Pilliet,<sup>292</sup> Koster,<sup>201</sup> Lubarsch,<sup>228</sup> Bakacs,<sup>27</sup> Vietsoldt,<sup>748</sup> Straus and Gamaleia,<sup>339</sup> Goldzieher and others. Arnold<sup>8</sup> was the chief advocate of fragmentation of the nuclei. In an effort to settle the question of nuclear division in giant cells, Wakabayashi<sup>356</sup> working under Benda's direction studied certain inclusions in giant cells with Heidenhain's iron hematoxylin and a method devised by Benda. He demonstrated certain bizarre spheroids

in giant cells fixed in Flemming's solution, which he interpreted as pathologic centrosomes and centrospheres. His observations were confirmed by Heixheimer<sup>158</sup> and by Heixheimer and Roth,<sup>159</sup> and questioned by Joest<sup>174</sup> and others, who suggested that they were probably Wolbach's inclusions.

*The Formation of Giant Cells by Fusion of Cells*—The fusion theory has been the most widely adopted of all the theories of the formation of giant cells. The earlier arguments in its favor were based chiefly on the absence of mitotic figures. Some authors applied the observation of fusion of phagocytes in starfishes, reported by Metschnikoff and Adam,<sup>1</sup> and a similar observation made on frogs by Lange<sup>209</sup> to pathology in human beings. Arnold, who favored fusion, as well as nuclear fragmentation, believed that the mosaic arrangement of the nuclei suggested fusion. Langhans, as has already been stated, favored fusion because of the platelike arrangement and similarity of the nuclei of the adherent "cell mantels." Krause<sup>202</sup> thought that if nuclei multiplied by division, they should occur in even numbers, which they were not likely to do by actual count.

More recently, Mallory<sup>241</sup> explained fusion on the basis of over-stretched surfaces of phagocytic cells and changes in surface tension. Wells<sup>377</sup> also explained the formation of giant cells as a combination of chemotactic phenomena and changes in surface tension. He stated that the cells, especially those of the reticulo-endothelial system, move toward an attracting particle, and when that particle is large, the cells spread out on its surface, and their contents of cytoplasm flow together because of their altered surface tension. The peripheral position of the nuclei depends on the fact that, in ameboid motion, the nucleus is entirely passive, is dragged along by the cytoplasm and, hence, is farthest from the attracting particle. Ziegler,<sup>388</sup> Boirel,<sup>43, 14</sup> Ley,<sup>217</sup> Lange,<sup>209</sup> Wechsberg,<sup>367</sup> Mallory,<sup>242</sup> Forbes,<sup>108</sup> Burgess,<sup>59</sup> Wells<sup>377</sup> and others favored fusion of white cells generally. Weiss,<sup>373</sup> Walb<sup>377</sup> and Ewertski<sup>95</sup> worked on exudates in the cornea, and concluded that giant cells were formed by the fusion of white corneal corpuscles, and Senftleben<sup>329</sup> using similar methods, included lymphocytes in the fusion as well. Schuppel,<sup>326, 28</sup> Birch-Hirschfeld<sup>77</sup> Ribbert,<sup>700</sup> Bredichin<sup>48</sup> Klebs,<sup>188</sup> Mai,<sup>276</sup> Franchetti,<sup>110</sup> Kiener<sup>185</sup> and others believed in the fusion of fixed endothelial cells, and Schmauss and Urshinsky in the fusion of epithelioid cells. Wallen<sup>359</sup> applied Bielschowsky's silver method, and demonstrated a reticulum in giant cells similar to that between the pre-existing surrounding cells, this, he thought, indicated fusion. Lambert<sup>207</sup> Cohen,<sup>69</sup> Lewis<sup>220, 221</sup> and Maximow<sup>278</sup> observed fusion actually taking place in tissue cultures.

Haythorn<sup>110</sup> and Permar<sup>286</sup> favored fusion on the ground of the distribution of the phagocytosed granules of carbon. Kaisner and Meyers<sup>180</sup> reported the fusion of alveolar epithelial cells to form giant cells in organizing pneumonia and Waldstein<sup>255</sup> described a fusion of epithelial cells in the germinal tubules. Numerous others, who accepted other views included fusion as an alternate possibility.

*Formation by Combined Nuclear Multiplication and Fusion*—Several authors favored the theory that giant cells were formed by combined nuclear division and fusion of cells, while others believed that one process could take place at one time and the other at another.

Metschnikoff<sup>266</sup> described fusion in *Bipinnaria* and in *Astropecten*, and applied the theory generally until he studied tuberculosis in a small gopher-like animal the Ziesell, here he found nuclear multiplication evidenced by mitoses. Stschnastny<sup>41</sup> one of his pupils, repeated his experiments on the Ziesell, also found evidences of nuclear multiplication, saw a mitotic figure and so concluded that the formation of giant cells was different in varying species. Adam<sup>1</sup> made a distinction between those mesothelial cells about foreign bodies in the body cavity of the astropecten which multiplied to form a "plasmodium" and those which fused to form a "syncytium." Manasse,<sup>216</sup> Marchand<sup>210</sup> and Heizog<sup>161</sup> found that epithelioid cells in early tuberculosis often contained mitotic figures and that these cells were easily differentiated up to the two-four-eight nuclear stage. They evolved the theory that multiplication took place until the cells became large enough to produce an attractive force after which they fused with similar cells to form giant cells. Kostenitsch and Wolkow<sup>200</sup> thought phagocytes wandered into free foci of plasma exudate proliferated, at first and later fused to form giant cells. Joest (cited by Stschnastny<sup>41</sup>) favored fusion but thought either could happen. He said that the lymphocytes did not fuse to form giant cells and that when they were present within giant cells, it was due to their having been phagocytosed. Bakacs described two stages in the formation of giant cells one of primary degeneration and a later stage of nuclear proliferation. He thought that the presence of giant cells indicated a progressing lesion and then absence a healing one.

*Additional Theories of the Formation of Giant Cells*—Kockel<sup>111</sup> discussed the relative merits of fusion and nuclear division at some length, and while he favored fusion he suggested a rather novel way of accounting for it. He pointed out that dead cells were known to be phagocytosed by living cells and also that Kiuckmann<sup>204</sup> had shown that living cells might penetrate dead cells so that one possible way in which fusion could come about was for the more active one of two giant cells to phagocytose the other. Similar views have been expressed since

Guéysse-Pellissier<sup>129</sup> suggested that when single cells died, then chromatin was broken up and extruded, and was then reabsorbed by giant cells and formed into new nuclei.

Several authors suggested that giant cells were not true cells, but in reality only artifacts resembling cells. E. Wegner<sup>165</sup> and Arnold<sup>9</sup> thought some giant cells were formed by sudden areas of degeneration in the centers of groups of cells. Kostenitsch and Wolkow suggested that giant cells might be nothing more than areas of coagulated plasma, either in the connective tissues or in vessels, and that the appearance of being a giant cell was due to separate cells which wandered into the periphery of the plasma zone and underwent proliferation. If this were the case, the size, shape and appearance of the so-called giant cell would depend on the pressure and comparative rigidity of the surrounding tissues. Medlar<sup>261</sup> recently published an opinion somewhat similar. He considered that the giant cells of tuberculosis did not appear until after necrosis had set in. He studied their formation with human, avian and bovine strains, and concluded that, in each instance, areas of necrosis developed and were invaded by mononuclear leukocytes, lymphocytes and polymorphonuclear leukocytes. The infiltrating cells might pass to the centers of the dead inflammatory tissue or remain in the borders, giving the typical appearance of peripheral or central arrangement of nuclei, respectively. He stated definitely that giant cells in tuberculosis were not cells, but only infiltrated caseous foci.

When Medlar reported his views, I was studying the effects of edema on tuberculous lesions in rabbit ears and at once I turned my attention to his observations. I found that where edema or a serous exudate was produced in early tubercles formed in tissues marked with india ink, the giant cells separated in one of two ways: some separated out as sharp cellular structures with definite outlines, showing them to be true cells, while others broke up and separated out as fragments of necrotic tissue with single and smaller multinucleated cells. I think Medlar's idea explains a stage of the formation of giant cells, but is limited to a step in development. The majority of tuberculous giant cells are true cells.

The various theories which accounted for giant cells on the basis of their resemblance to cross sections of vessels and associated characteristics have already been discussed.

#### METHODS USED IN STUDIES OF GIANT CELLS

The methods used in studies of giant cells have embraced almost all the procedures known to pathologists. Beginning with the examination of unstained smears and teased preparations, and progressing through the simple staining of sections of tissues embedded in celloidin, the special staining of sections from tissues prepared in paraffin, the experimental production of lesions known to produce giant cells, the vital

staining of tissues and the cultivation of tissues in vitro—each new method has added something to the knowledge not only of the giant cell, which in itself is comparatively unimportant, but to the knowledge of the nature of the related diseases and of the bodily means of resistance and defense

It is my purpose to review briefly the methods used and cite, when possible, the main fact or facts which each method has uncovered

*Fresh Preparations*—Giant cells were first described in smears, teased preparations and scrapings mounted in physiologic sodium chloride solution, in glycerin or in weak acetic acid. Langhans<sup>211</sup> reported his results with fresh tissues, and demonstrated that giant cells are not necrotic foci with cellular infiltration, but true multinucleated cells. Metschnikoff<sup>201</sup> and his followers studied phagocytosis by macrophages in fresh preparations and smears, and contributed the fundamentals of giant cell function. Koch<sup>104</sup> described the presence of bacillary masses in stained smears, and almost all authors who have worked with intraperitoneal inoculations of tubercle bacilli have made cytologic studies of the exudate as a part of the work. These methods are all useful and receive altogether too little attention at present.

*Sections of Fixed Tissues*—By far the greater number of studies reported have been of fixed tissues. These studies have added much of the accurate knowledge which is at hand, and some of the confusion which exists. Limited at best, the study of fixed tissues has been further hampered, in innumerable instances, by the use of more or less inefficient fixatives and imperfect staining methods and by the inadequate training of some of the observers. Much of the early work was done by simple nuclear staining with carmine. Later, hematoxylin became the vogue, and has held its place to this day in many laboratories. Eosin, erythrosin, phloxin and azure II have been the more commonly used counterstains, though none of them is differential for blood or tissue cells. Mallory<sup>-10</sup> introduced the use of eosin-methylene blue on tissues fixed in Zenker's solution and more recently advised a change to phloxin-methylene blue. In my experience, this method has been the most valuable for the study of giant cells and other forms of exudative cells. Because of its polychromatic staining of the cytoplasm of the lymphocyte-plasma cell series, one is able to distinguish clearly this series of cells from the large, nongranular mononuclear leukocytes, and to detect the differences between the nuclei which characterize the multinucleated giant cells and those of lymphocytes or plasma cells which may have been phagocytosed. Giemsa's stain has been used for similar purposes, but is not easily applied successfully to tissues.

The special stains which have been applied to the nucleus have been used to bring out the nuclear changes which have to do with nuclear

division, and have been made for the purpose of settling the question of fusion or division. Heidenham's hematoxylin (Schmorl<sup>323a</sup>), Benda's hematoxylin (Schmorl<sup>323b</sup>) and Benda's special stain to bring out structures connected with nuclear changes, centrosomes and centrospheres (Schmorl<sup>3-3c</sup>) were used by Wakabayashi,<sup>156</sup> Heixheimer,<sup>158</sup> Heixheimer and Roth<sup>159</sup> and Heizog<sup>161</sup> with more or less divergent conclusions, as already has been noted.

Chemical reactions for iron, fat crystals, soaps, glycogen, collagen, colloid and elastic tissue were used by Heixheimer, Wolbach, Iwanoff and others in an attempt to identify certain inclusions which they encountered.

Modifications of the Gram-Weigert and of all the acid-fast bacterial stains have been used in the study of the included organisms and the yellow central bodies described as masses of dead tubercle bacilli by Weigert and Koch. Through the use of connective tissue and fibril stains, such as Mallory's stain for connective tissue, phosphotungstic acid hematoxylin, Bielschowsky's silver method and Van Gieson's stain, it has been possible to show that giant cells may include collagen fibrils. Weigert's stain for elastic tissue has shown that fibers of elastic tissue may become potent foreign bodies leading to the development of giant cells. The stains for reticulum were used to advantage by Downey,<sup>80</sup> Warren,<sup>359</sup> Foot,<sup>103</sup> and others in their studies of reticulo-endothelium. Mallory and Parke<sup>44</sup> employed similar methods to show that endothelial cells do not form reticulum.

Many attempts were made to differentiate tuberculous giant cells from osteoclasts, and while it was sometimes possible to show acid-fast organisms in one, and alkaline granules in the other, a consistently reliable method has not been found, and this is an additional point for their cytologic identity.

*Vital Stained Tissue.*—Vital staining has added a great deal to our knowledge of tuberculosis, the formation of foreign body cells and exudative lesions generally. The first account of vital staining which I found was that of Walb,<sup>57</sup> who injected the cornea of rabbits with carmine solution and found that the corneal corpuscles became stained, while the leukocytes did not take up much carmine. He traced the formation of foreign body giant cells from the stained corpuscles. Senfleben<sup>329</sup> and Emil Marchand<sup>249</sup> performed similar experiments, but did not confirm Walb's conclusions. F. Marchand<sup>250</sup> injected gelatin stained with methylene dyes, and produced foreign body giant cells containing stained phagocytosed particles. Oppenheimer,<sup>274</sup> Goldmann<sup>127</sup> and Bowman, Evans and Winternitz<sup>71</sup> studied the formation of tubercles from vitally stained Kupffer's cells in the liver. Haythorn,<sup>1</sup> and later Foot<sup>101-107</sup> and Peimar,<sup>285</sup> injected india ink in studying the formation of tubercles and giant cells. McJunkin<sup>231</sup> marked

mononuclear leukocytes with finely ground lamp black Sewell,<sup>100</sup> Peimar<sup>284</sup> Simpson,<sup>11</sup> Foot, Sabin M R Lewis and W H Lewis<sup>219-222</sup> and others used pyrrhol blue neutral red, trypan blue trypan red, colloidal carmine, Niagara blue, isamine blue and the benzidine reaction in identifying the large mononuclear leukocytes Gardner<sup>116</sup> and Cash<sup>61</sup> separately devised ways of studying cells vitally stained with neutral red in paraffin sections

By means of these methods of vital staining it has been possible to relegate the activities of fixed tissues to the background in the formation of giant cells and to emphasize the importance of the large mononuclear phagocytic cells

*Experimental Studies*—The most interesting work which has been done on giant cells is that along experimental lines One of the earliest groups of experiments in which giant cells were found was performed by Conheim and Frankel<sup>7</sup> in 1869 Apparently they were interested in giant cells only as one of the diagnostic points of tuberculosis They transplanted bits of caseous material into the peritoneal cavities of guinea-pigs, and obtained tubercles They then took bits of normal tissue from tuberculous cadavers, and again obtained tubercles The work preceded the days of sterilization of instruments and after they had injected all sorts of things, including blotting paper, clean lint, gutta serena, india rubber and the like, they obtained tubercles with giant cells in all the animals which survived acute general peritonitis They decided from their experiments that tuberculosis was not due to a specific virus, but came from a variety of substances Lange<sup>109</sup> studied the reactions in the lymph sac in frogs, and found giant cells Weiss,<sup>173</sup> after finding giant cells about coal dust and in a syphilitic bubo, injected hairs woolen fibers and feathers into the subcutaneous tissues of animals and studied the process of encapsulation He found rather large cells with single nuclei about the foreign substance They suggested epithelial cells, but were not, and some of them had from two to four nuclei There were also well developed giant cells which he thought came by fusion of the smaller ones

Ziegler's<sup>186</sup> experiments with glass platelets have already been discussed Emil Maichand,<sup>249</sup> in 1883, working under the direction of Baumgarten,<sup>5</sup> implanted silk sutures and sponges in the tissues of guinea-pigs He used two series, one with iodoform crystals and one without He noted that organization of the sponge took place by the extension of connective tissue and capillaries into the meshes and decided that giant cells came from the ingrowth of fixed tissues The giant cells appeared in the peripheral areas of the sponge, while the infiltrated areas were in the more central portions He also repeated Walb's<sup>157</sup> and Senftleben's experiments with modifications Walb, in 1876 had injected the cornea of living rabbits with carmine solution, and



found that ordinary white cells and lymphocytes were not stained, but that true corneal corpuscles took up the carmine. He traced giant cells to the fusion of the stained corneal corpuscles. Senfleben, in exactly similar experiments, had concluded that they came from fused lymphocytes. E. Marchand injected the cornea of a dead rabbit, removed it and used it as a foreign body in another animal. In two days, all the pus cells about it were stained with carmine, he therefore thought the method inconclusive. E. Marchand verified the observations of Baumgarten as to the relationship of giant cells to blood vessels, and concluded that giant cells are always formed from fixed tissues.

Hallwachs<sup>130</sup> was one of the early workers to use antiseptics to exclude the inflammatory reactions in the healing of injuries caused by various foreign bodies. Other early experimenters included Heidenhain (quoted by Langenbeck<sup>130</sup>), who injected elderpith, von Recklinghausen<sup>137</sup> and Ranvier,<sup>137</sup> who injected blotting paper and a substance called "Lammanastuke," and von Lesser,<sup>138</sup> who reported on the reactions formed about catgut sutures.

Felix Marchand, in an important contribution in 1888, injected sponge, small pieces of the hardened lung of a human being in place of a very firm sponge, hardened liver, pieces of cork, blotting paper, rabbits' cornea and stained gelatin. Marchand<sup>130</sup> found sponge of fine grain the best material for the study of giant cells, and credits Hamilton<sup>134</sup> (1881) with having been the first to use it. Marchand<sup>130</sup> made many experiments, including the injection of stained gelatin and lycopodium spores, and concluded that giant cells came in part from the cells in the immediate surroundings, and possibly also from wandering cells. He credited Martin<sup>135</sup> with first using lycopodium spores. Later, von Bunge, working under Marchand, used foreign bodies dipped in turpentine or iodoform and verified Marchand's observations. Herzog,<sup>161</sup> another of Marchand's pupils, repeated the experiments with sponge grafts in 1916, saying that he wished to study the results with modern technical methods and modern differential staining, and in the light of recent conclusions with reference to blood cells. He concluded that foreign body giant cells came from mononuclear leukocytes, serosal mesothelium and connective tissue cells in the submesothelial areas, and resulted from nuclear proliferation.

Faber<sup>97</sup> first injected agar-agar. Forbes,<sup>108</sup> working under the direction of Mallory and Wolbach, studied the origin of foreign body giant cells about injections of agar-agar. In 1922, I<sup>139, 140</sup> made some experiments by injecting stained agar-agar, agar-agar mixed with lycopodium spores and agar-agar mixed with lycopodium spores stained, before injection with gentian violet. I injected india ink to mark the cells, and it seemed to me that giant cells in these foci were formed by the fusion of mononuclear phagocytes. Later I produced lesions in

similar ways, and followed them by inducing localized edemas or serous exudates about them. I was interested in separating the tubercles, and particularly the giant cells, into their constituent elements. Some giant cells broke up into a central caseous mass with a margin of phagocytes and other cells, as stated by Medlar<sup>201</sup> but the majority of the giant cells separated out as definite cellular entities.

No other type of foreign body has been used in the production of giant cells so frequently as tubercle bacilli and their products. It is impossible to review the experiments here, though the results of many have been given. Particularly worthy of mention is the experiment of Kostenitsch and Wolkow,<sup>200</sup> who produced chronic inflammatory exudate of mononuclear cells by injections of albumin before the injections of tubercle bacilli. Also worthy of mention is the work of Pruden and Hodenpyle,<sup>204</sup> who were the first to show that giant cells are formed in lesions produced experimentally by the injection of dead tubercle bacilli. Of interest also, was the experiment of Bugess,<sup>59</sup> who injected the chemical constituents of caseation necrosis synthetically prepared by mixing calcium phosphate, calcium carbonate, cholesterol, palmitic and stearic acids and several bland oils and fatty substances extracted from tubercle bacilli, and obtained giant cells, thus showing conclusively that the giant cell of the tubercle is only a type of giant cell and not a specific structure.

*Tissue Cultures*—Awiorow and Timofejewski<sup>17</sup> paved the way for the study of cultures of blood cells *in vitro*. In the hope of settling the question between fusion and nuclear division, many workers turned to this field. The possibility of fusion to form giant cells has been definitely settled, so far as embryonic cells and the cells of some of the lower animals are concerned, but the observation of giant cells in cultures has not always led to uniform conclusions. Several research workers, who formerly believed that giant cells were formed exclusively by direct nuclear division, later reported the observation of fusion. Lambert and Hanes<sup>206</sup> observed giant cells of great size, from 30 to 500 microns in diameter, in cultures of spleen and bone marrow of rats. They interpreted the cells as the result of unsuccessful cell division. In 1912, Lambert,<sup>205</sup> in studies of cultures of the spleens of embryo chicks, reported the observation of a fusion of cells to form the large giant cells. In 1921, Lewis and Webster,<sup>223</sup> working with cultures of human lymph nodes, described the formation of giant cells by amitosis from endothelial cells which corresponded to the reticular cells of Maximow. Lewis and Lewis<sup>222</sup> stated definitely that, in cultures of human lymph nodes, giant cells were not formed by fusion. Subsequently, Lewis and Bruda<sup>221</sup> observed a fusion of mononuclears to form large giant cells, and still more recently in 1927, Lewis,<sup>220</sup> in cultures of rat sarcoma reported the formation by fusion of giant cells in all respects typical of

the Langhans giant cell of tuberculosis. He published a series of sketches made at intervals of from fifteen to twenty minutes, which illustrated the fusion. In the same cultures, he observed direct nuclear division without division of the cell. Giant cells appeared in his cultures to be formed, in part, by direct division, mitoses not having been seen, in part, by fusion of separate cells, in part, by the incorporation of additional single cells with the giant cell, and in part, by the fusion of two or more multinucleated giant cells to form larger giant cells.

Cohen,<sup>64</sup> using Sabin's<sup>313</sup> technic with neutral red, studied cultures of turtle's blood and saw cells fuse to form giant cells. Later he found that giant cells may break up and form smaller multinucleated cells. Maximow<sup>257</sup> studied the formation of giant cells in tissue cultures to which tubercle bacilli had been added, and found that tubercles were formed from "polyblasts," which he stated were the same cells as the "macrophages" of Metschnikoff. He stated that these cells originated, in part, from resting wandering cells of the connective tissues and, in part, from nongranular white cells and monocytes. He observed the transformation of polyblasts into epithelioid cells and giant cells. The latter were formed by the fusion of epithelioid cells. Lang,<sup>207</sup> working with cultures of rabbit lung and tubercle bacilli, traced the formation of tubercles to the interalveolar septal cells, but did not observe any formation of giant cells.

Analyzing the evidence from tissue cultures, I find that the formation of giant cells by fusion cannot be excluded, and it seems probable that direct nuclear division, though much harder to prove than fusion, also occurs.

*Reconstruction*—Medlar presented some interesting serial section reconstruction models of giant cells at the Meeting of the International Museums Society in Albany in 1926.\*

#### FUNCTIONS OF GIANT CELLS

The earliest idea of the function of the giant cell was that held during the period dominated by the "blastema" theory of cell origin. Giant cells were then supposed to be centers for the spontaneous development of exudative cells. According to Langhans, Rokitsansky<sup>307</sup> described giant cells in his treatise on pathology as "mutterzellen," or large multinucleated protoplasmic structures with many free mononuclear cells gathered about them. They were believed to act as small "pseudo-peritoneal" membranes and to produce tubercle cells spontaneously. This view was practically given up with the general adoption of Virchow's theory, "omnis cellula e cellula."

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\* The Bulletin of the International Museums Society containing a report of the Albany meeting has not yet appeared.

Metschnikoff<sup>267</sup> maintained from the beginning that giant cells were multinuclear phagocytes, and that they originated from unicellular phagocytes. This view has now come to be almost universally adopted. Opposed for many years to this view were the theories of Baumgarten<sup>28, 30</sup> and Weigert,<sup>372</sup> which postulated that giant cells were primarily centers of destruction and were doomed from the moment of their appearance. It followed from this hypothesis that giant cells did not have a function, but were only stages in necrotic changes. Even Weigert, however, described yellow nodular inclusions in giant cells which he believed to be dead bacilli. Other theories have attributed ameboid motion to giant cells, which permitted them to wander about and distribute tubercle bacilli. Schmaus and Ushinsky<sup>319</sup> considered them as centers for the beginning of a tubercle. The present interpretation connects them with the incorporation of necrotic matter, crystals and anything insoluble which is deleterious to the tissues and is absorbed either slowly or not at all. On account of this phagocytic activity, Smith<sup>142</sup> considered giant cells as evidence of the highest resistance of a tissue against tuberculosis.

There is no longer any question that the chief function of giant cells is one of defensive phagocytosis. Zinsser<sup>391</sup> credited Panum<sup>280</sup> with having been the first to suggest that phagocytosis plays an important rôle in combating infectious diseases. Metschnikoff<sup>267</sup> was the real founder of the school which taught that phagocytosis was the body's chief mechanism of defense. He divided phagocytes into fixed and ameboid phagocytes. The fixed type were lining cells, for example, Kupffer's cells, the ameboid type consisted of (1) microphages, or polymorphonuclear leukocytes, and (2) macrophages, or mononuclear phagocytes. Metschnikoff thought that giant cells were an active mechanism of defense against tuberculosis, that they developed from the macrophages and that they were themselves active ameboid phagocytes. Stschnastny, one of Metschnikoff's pupils, said that giant cells devoured tubercle bacilli by their very voracity and that, though the bacilli multiplied when first taken up, they were eventually destroyed. Di Renzi<sup>299</sup> concluded from his researches on giant cells in tuberculosis that the bacilli were taken in and underwent multiplication for a time, but that later waxy capsules formed about them, and these became fused into yellow clumps of dead bacilli. Koch<sup>194</sup> also described the waxy yellow inclusions and interpreted them as dead organisms. He did not consider that the result was in any way due to the activity of the cell. Welcker studied phagocytosis of tubercle bacilli on the warm stage and found that the cells took up bovine bacilli quickly and underwent caseation, but that they phagocytosed human and avian strains much more slowly. With reference to streptococci, Gav and Morrison<sup>121</sup> considered phagocytosis to be the chief agent of defense. Bonnel<sup>1744</sup>

and Kiener<sup>183</sup> were also advocates of phagocytosis by giant cells as an important defensive reaction. Kockel<sup>195</sup> believed that giant cells phagocytosed not only tubercle bacilli and exudative cells but also each other. Lange<sup>209</sup> observed phagocytosis of cells by multinucleated cells in puncture fluids from the lymph sac of frogs.

Karsner,<sup>179</sup> in his new textbook, outlined phagocytosis briefly in three phases: (a) the stage of approach, which he attributed to chemotaxis, (b) the stage of ingestion due to mobility of the phagocyte, stickiness of the cell wall and changes in the surface tension and in the hydrogen ion concentration, and (c) the stage of destruction or digestion of the particle. Formerly, there was some doubt as to the power of a cell to digest incorporated material. Faber,<sup>97</sup> in 1893, demonstrated the power of giant cells to digest agar-agar. The preparations of Ssudakawitsch, showing digestion of elastic fibers, were convincing, some of the elastic fibers were long enough to extend beyond the borders of the cell and such extracellular portions were preserved, while the intracellular parts were partially digested. Opie<sup>273</sup> demonstrated the enzymatic action of phagocytes on tubercle bacilli. Maximow<sup>257</sup> followed the formation of tubercles in cultures of mammalian tissues and observed the phagocytosis of tubercle bacilli and their subsequent digestion. He stated that the intracellular digestion of bacilli in epithelioid cells is probably highly increased after their fusion into giant cells, so that the number of organisms in the multinucleated cells is never great. Later, the giant cells contain inclusions of yellow pigment resulting from destroyed bacilli. Wells<sup>377</sup> stated that, in general, the digestion of materials taken into a giant cell seems to go on just as it would in the individual cells which compose it. Unless the particle is insoluble, the digestion takes place by the action of intracellular enzymes. If the chemical substances are inert, they may remain in the cells for long periods.

Phagocytosis is a function of cell protoplasm, and the surface of a phagocyte is readily adjustable and easily permeable. It is not difficult to see how two such cells, either one of which is capable of incorporating a foreign body of a size nearly equal to itself, may under proper conditions fuse to form a cell with two nuclei.

The functions, in addition to phagocytosis, which have been attributed to giant cells, have been those of distributing infectious agents and of protection. Stschnastny<sup>341</sup> thought that giant cells were active agents in distributing tubercle bacilli, which they had phagocytosed in carrying them to new foci. Rous and Jones<sup>300</sup> believed that, at times, cells of living tissues protected *Leishmania*, gonococci, *Bacillus leprae* and *Bacillus tuberculosis* against the destructive action of the body fluids. They demonstrated the protection of *Bacillus typhosus* in vitro by phagocytes. Giant cells probably have the same quality of protection.

as single phagocytes. The fact that they completely engulf crystals and sharp irregular particles seems to indicate that they may serve also in protecting the more delicate tissue cells from injurious particles.

The ingestion of inert particles, such as glass and carbon, has not been satisfactorily explained. The assumption that they become coated with serum which serves as food for the phagocyte is not in itself satisfactory, since the cells themselves are in a medium of serum which surrounds them on all sides.

#### FATE OF GIANT CELLS

Comparatively few authors have discussed the fate of giant cells. Weigert<sup>372</sup> considered them necrotic from the beginning, and as resulting not only in their own destruction, but also in the death of the other cells in the area. Franchetti<sup>110</sup> stated, on the other hand, that giant cells could remain in the tissues for long periods without either degenerating or changing back into connective tissue cells.

The final disposition of giant cells probably depends largely on the relative inactivity of the substances which brought about their formation. For instance, in a section in my possession, showing giant cells about silk sutures which had been placed in the dura at operation more than two years before the patient came to autopsy, the giant cells appear intact and healthy. This does not mean, of course, that they are the same giant cells originally formed at the site, but it does suggest that they are rather permanent structures. In tuberculous, anthracotic lungs, giant cells with circles of carbon pigment about the nuclei are commonly seen in the margins of healed, encapsulated caseous lesions. Sometimes they are the only nucleated cells in the area, which indicates that they have outlived the surrounding tissues. The presence of the phagocytosed pigment suggests that they are not recently formed cells, because most of the free pigment has disappeared from the area. Hence, it seems likely that giant cells may persist for long periods about foreign substances, and that they may even remain active, living cells until the degeneration or death of the other tissues in the region.

As for the fate of giant cells after the substances which attracted them are gone, the story may be different. Hektoen<sup>148 149</sup> studied the breaking up of giant cells in a case of healing tuberculous meningitis, and found the giant cells fibrillating, splitting up and dividing into mononuclear cells. He followed up his observation with some experiments on the absorption of coagulated serum from the anterior chamber of the rabbit's eye, and concluded that in healing, nondegenerated tuberculous tissue, the multinucleated giant cells may, in part, disintegrate and undergo absorption, and in part form viable small cells. Cohen,<sup>69</sup> in his observations of cultures of turtle blood, not only witnessed the formation of giant cells by fusion, but also saw some of them break up into several smaller multinucleated giant cell masses.

## THE OCCURRENCE OF GIANT CELLS

Giant cells may be found in any tissue of the body or in any kind of lesion which persists for more than the eight to fourteen days necessary for their development. Whenever there is an insoluble or slowly soluble substance too large to be ingested by a single cell, a giant cell will sooner or later appear. The substance may be extraneous material artificially or accidentally introduced, or it may be coagulated blood or exudate, or necrotic bodily tissue, the result of injury, of improper nourishment or of enzymatic action. The attempt to review their occurrence is limited to the more common and constant lesions in which they are found, and to a few unusual sites.

*In Simple Granulation Tissues*—Lubarsch<sup>229</sup> described the presence of giant cells in simple reparative granulations. He pointed out that they were there for the resorption of hemorrhage, hemoglobin pigment, coagulated bits of fibrin, injured elastic fibers and like matter. Langhans<sup>212</sup> did his first work on phagocytosis by giant cells on the resorption of hemorrhage. Ssudakawitsch,<sup>333</sup> Unna,<sup>346</sup> Jores,<sup>176</sup> Hektoen<sup>151</sup> and others described giant cells about elastic fibers. Mallory<sup>242</sup> stated that they may form about collagen fibers and Goldzieher and Makai described them in the borders of infarcts and other like lesions. As examples of their occurrence in chronic inflammation, one may cite the presence of giant cells in the bronchioles in asthma, observed by Marchand,<sup>251</sup> in bronchiolitis obliterans, witnessed by Vogel,<sup>351</sup> and in organizing pneumonia, reported by Karsner and Myers<sup>180</sup>.

*In Areas of Degeneration, About Deposits and in Foci of Necrosis*—Giant cells have been described as occurring about both epithelial hyalin and connective tissue hyalin by Kruckmann, Kiause, Manasse and Mallory, and about areas of amyloid by Kruckmann. Rhea (cited by Forbes<sup>199</sup>) found them about degenerated colloid masses in the thyroid, and Wiesel<sup>379</sup> in hyaline areas of the thymus. They are commonly found about deposits of calcium salts and about all kinds of crystals. C. Meyer,<sup>267</sup> Manasse, Kruckmann, LeCount<sup>214</sup> and others described giant cells filled with cholesterol crystals, or interpreted the clefts found in the cells as having contained cholesterol crystals prior to the passage of the tissues through alcohol. Manasse,<sup>245</sup> Korner,<sup>199</sup> Friedrich and Kirchner<sup>184</sup> and Janssen (quoted by Grunert<sup>128</sup>) reported giant cells in the so-called cholesteatomas of the ear, and Klemm<sup>191</sup> found them in a large, cholesterol filled cyst of the omentum. They are also common about fatty acid crystals, as pointed out by Herxheimer,<sup>155</sup> Mallory<sup>242</sup> and others. In one of Klotz's class sets of sections, numerous giant cells are shown about bile pigment and fatty acids. I have frequently seen them in areas of fat necrosis of the pancreas and peritoneum. Weber<sup>368</sup> produced them in subcutaneous fat by the injection of ether. They have been found about uric acid crystals and around

chalk stones in gout I observed a remarkable case in which giant cells were numerous about the corpora amylacea in the prostate, and they are common about the similar structures in psammomas

*About Foreign Bodies*—Giant cells are found about all sorts of inert foreign bodies, as has been shown by the experimental work already cited They were found early by Marchand and von Lesser<sup>218</sup> about catgut and silk sutures They are found regularly about fatty, oily and paraffin masses injected for cosmetic purposes, and have been described as occurring in paraffinomas by Firkets<sup>100</sup> and others I have seen them about several substances not yet mentioned, including gunpowder in burns, particles of carbon, glass, pieces of coal driven into the wounds of miners, and in a sinus which was under treatment with bismuth paste

*In Tuberculosis*—So much has already been said about giant cells in tuberculosis that little more than a summary need be added Reviews of the early literature were made by Durck,<sup>86</sup> Durck and Oberndorfer,<sup>87</sup> Pertik,<sup>288</sup> Paltauf<sup>277</sup> and Kockel<sup>195</sup> The predominant opinion about giant cells in tuberculosis at present is that they are identical with the foreign body giant cells which arise either from epithelioid cells or from wandering nongranular leukocytes The stage of their formation presented in cells with two or three nuclei is the one about which the least seems to be known If they are foreign body cells, the particles causing them to form must be extremely small and rarely acid-fast tubercle bacilli Many who have accepted the fusion theory for larger cells have adhered to nuclear division for the smaller ones Medlar's idea that giant cells are agglomerations of separate cells in caseous foci does not explain this stage of few nuclei, nor the final large globular cells The Baumgarten-Weigert idea of giant cells as centers of necrosis may be correct in some instances, but cannot be applied universally Bakacs' statement that giant cells indicate a progressive lesion, and their absence a healing one, will not hold Isolated giant cells are often present in the borders of inactive, totally calcified, fully encapsulated lesions

Stewart and Rhoads<sup>335</sup> made an interesting observation with reference to the presence of giant cells in reactions of the skin to tuberculin They explained their presence on the basis of foreign body giant cells gathered about small focal areas of necrosis, and not as a specific response to tuberculin Weller<sup>376</sup> pointed out that foreign body giant cells unassociated with products of tuberculous infection may occur by accident of position in tuberculous lesions Waitkin<sup>362</sup> described typical tubercle giant cells in placental tubercles

*In Syphilis*—Giant cells were described as occurring in gummas by Jacobson,<sup>109</sup> in 1877 They had been reported in syphilis previously by Baumgarten,<sup>26a</sup> but were thought by him to be due to concurrent tuber-



culosis Later, Baumgarten <sup>26b</sup> reiterated his belief that giant cells were present in gummas only when tuberculosis also existed in the same lesion, and he pointed out that tuberculosis often coexisted with lymphosarcoma as well, which might account for their presence in sarcomas Maichand <sup>250</sup> disproved Baumgarten's claim by producing giant cells in all sorts of experimental lesions, and soon giant cells were reported in gummas of all parts of the body Brissaud,<sup>49</sup> Malassez and Reclus <sup>2 8</sup> and Schmaus and Sacki <sup>318</sup> reported them in syphilitic lesions of the brain, and Pick <sup>300</sup> found them in a gumma of the spinal cord Brodowsky,<sup>52</sup> Thoiel <sup>344</sup> and Busse <sup>62, 63</sup> reported them in gummas of the heart Brodowsky <sup>52</sup> thought they arose from angioplasts, and Busse believed they were metamorphosed muscle cells Bruch found them in five cases of skin syphilis Eisenberg saw them in a primary lesion, and Binder described them in congenital syphilis of the liver Von Langenbeck <sup>210</sup> reported an interesting instance of coexistence of carcinoma and gumma in the tongue, and observed the presence in them of numerous giant cells Herxheimer,<sup>157</sup> who reviewed the subject in 1908, pointed out the similarity between caseous and gummy necrosis, and said that if one accepted Weigert's theory of the formation of giant cells for tuberculosis, one might equally well apply it in syphilis He concluded that giant cells in syphilis, including both those with centrally placed and those with peripheral nuclei, were due to the action of the specific virus

It was formerly taught that a point in the differentiation of gummas from tubercles was the type of giant cell present Lubarsch,<sup>229</sup> in 1911, still adhered to this view It will not hold generally, and has been dropped from the more recent American textbooks Mallory <sup>242i</sup> stated that giant cells occur rarely in chancres and frequently in gummas, and that they are the same giant cells that form around elastic fibers, fat, its various products and fibrin Karsnei <sup>178</sup> stated that giant cells in gummas are of the same type as those in tuberculosis, but are less numerous In gummas of bone, in which syphilitic giant cells and osteoclasts occur together, it is impossible to tell one from the other unless by their relations to other structures

*In Miscellaneous Granulomas*—Giant cells have been found in nearly all infectious granulomas Duval and White <sup>88</sup> reported them in glanders, in which they thought that the cells developed by fragmentation of the nuclear chromatin Mallory said that the giant cells of glanders varied somewhat in nuclear structure from the ordinary forms of giant cells Eppinger <sup>91</sup> and Ducor <sup>85</sup> reported that they observed them in actinomycosis, in which their presence was confirmed by Lubarsch <sup>229d</sup> and Mallory McCallum stated that they are rarely found in actinomycosis, and I have failed to find them in several cases outside the bone lesions

Ricketts<sup>302</sup> reviewed the literature on oidiomycosis and blastomycosis, and reported twelve new cases of oidiomycosis. Giant cells were a constant observation in his cases, and his plates showing giant cells about the organisms are most beautiful. Hektoen,<sup>170</sup> Busse<sup>62</sup> and others found them in blastomycosis, and I have had several cases, unreported, in which the giant cells filled with budding yeast forms furnished the differential point of diagnosis. Giant cells have been described as occurring in rhinoscleroma and mycosis fungoides by Lubarsch,<sup>220d</sup> in Madura foot by Vincent<sup>340</sup> in paschachurda by Ssudakawitsch<sup>333</sup> and in the tissues about abscesses due to *Sporotrichum schencki* by Hektoen and Perkins<sup>152</sup>. Jadassohn<sup>170</sup> found them in erythema exudativum multiforme and nodosum, and Phillipson<sup>280</sup> in erythema multiforme. Permar and Weil<sup>287</sup> described giant cells as occurring in the skin lesions of a case of tularemia in man. An interesting and rather unusual lesion in which giant cells were a prominent feature was described by Warrin and Davis<sup>363</sup> in their report of pseudotubercles of the skin due to cactus spines.

*In the Vicinity of Animal Parasites in Body Tissues*—Animal parasites and their ova are sometimes the foreign bodies which lead to the development of giant cells. Paltauf,<sup>277</sup> Wagenmann,<sup>375</sup> Schroeder and Westphalen<sup>325</sup> and others reported them about cysticerci. Lehne,<sup>215</sup> Kiuckmann,<sup>204</sup> Vierordt<sup>348</sup> and Guillebiau<sup>131</sup> found them near the walls of echinococcus cysts. Mallory<sup>212g</sup> said that they were common about encysted trichinae, and Hutchinson described them about the encysted ova of *Schistosoma haematobium* and *Schistosoma mansoni*. In some class material sent me some years ago by Hutchinson from Tanta, Egypt, I made a careful study of the formation of giant cells. I found great numbers of large giant cells both inside and around the empty shells of the ova and around the sides of them in rectal and bladder polypi. Mononuclear phagocytes appeared to have wandered into the small empty capsules through crevices in the walls, and later to have fused and formed large multinucleated giant cells.

*In Giant Cell Granulomas of the Peritoneum*—Occasionally, surgeons, on opening the peritoneal cavity, find the peritoneal surfaces studded with small, more or less discrete nodules. The condition has frequently been mistaken for tuberculosis or general carcinomatosis. Several different conditions may give rise to the appearance. Hertzler<sup>154</sup> and others have applied the term pseudotuberculosis to it, and have described it in several forms: (1) a bacillary form, which apparently is not a definite entity, (2) a foreign body form, and (3) a form following the rupture of pseudomucinous cysts. I have not found any of the so-called bacillary forms, but I have had instances of the second and third forms. In one instance, I was sent a nodule by Dr J. Alexander

for diagnosis by means of frozen sections. The nodule was from a patient supposed to have general carcinomatosis. I found a simple foreign body granuloma with most beautiful giant cells formed about bits of striped muscle and cellulose. The history revealed that the patient had been operated on two years before for a ruptured duodenal ulcer. Similar cases were reported by Marchand,<sup>250</sup> Hanau,<sup>136</sup> Cooper,<sup>73</sup> Guthrie,<sup>132</sup> C. Meyer,<sup>267</sup> and Oidway. Imbert, Cottalorda and Lagarde<sup>166</sup> reported similar lesions due to bits of lint and sponge left at operation. Corionni and Iatrou,<sup>77</sup> incising the stomachs of guinea-pigs, produced the condition experimentally.

A similar appearance may follow the organization of extensive fat necrosis. Here the giant cells form about small cystlike areas of degenerated fat and fatty acid crystals. I have had one such instance, and Herxheimer<sup>155</sup> reported a case in which the foci were calcified.

That the organization of pseudomucinous substances from ovarian cysts may take the form of foreign body granulomas has been shown by Eiger,<sup>89</sup> Frankel,<sup>111</sup> Werth,<sup>278</sup> Gottschalk,<sup>126</sup> and Polano.<sup>293</sup> This type of granuloma was reviewed by Merkel.<sup>262</sup>

Still another type may follow the organization of fatty substances and hairs discharged into the abdomen through the rupture of dermoid cysts. Instances of this type were reported by Knuckmann<sup>204</sup> and by Herzog.<sup>160</sup> The relatively common occurrence of these peritoneal conditions should not be forgotten by surgeons and pathologists associated with active surgical clinics.

*In Inflammatory Lesions of the Bones and the Joints*—Since the osteoclast is in all probability a foreign body giant cell in a special environment, and is a normal constituent of all embryonic and adult bones, it almost goes without saying that they are found in every type of lesion of the bone. They are important in the embryonic development of bones (Keibel and Mall,<sup>182</sup>) in the healing of injuries and fractures, taking up not only bone salts but blood pigment as well, and in the resorption of calluses and of bony excrescences. That they do not necessarily have their origin in bone tissue is shown by their appearance about transplants into subcutaneous tissues of dead bone and polished ivory.

McCallum,<sup>233d</sup> Malloy,<sup>242j</sup> and Katsner<sup>178</sup> described giant cells as constant observations in acute and chronic osteomyelitis, in infectious granulomas of bone, in rickets, in osteogenesis imperfecta and allied conditions, in osteomalacea, in osteitis deformans of Paget and in other conditions of the bone. Giant cells were found in arthritis deformans by Nichols and Richardson,<sup>272</sup> and they are usually present in all other types of arthritis. They are common in pyorrhea pockets about the teeth, and material obtained in cuetting tooth sockets

## THE GIANT CELLS IN TUMORS

The giant cells in tumors have been known since the work of Muller<sup>271</sup> in 1838. The confusion which existed concerning the origin and nature of giant cells generally was largely due to the recognition that the giant cells in tumors often differed widely from those in tuberculosis and in foreign body granulomas. Rustizky<sup>211</sup> and others reported giant cells resembling osteoclasts in sarcomas of the bone, and the term "giant cell sarcoma" came into use. Lubarsch<sup>226</sup> stated that among the earlier textbooks of pathology, Thoma's was the only one which described a giant cell tumor outside the bone, and his exception was that of a giant cell sarcoma of the breast. The mistake which was made was that of considering all tumors containing giant cells as being identical in origin. C. Meyer<sup>267</sup> and Ziegler<sup>389</sup> later pointed out the wide distribution of giant cells in tumors, and explained them on the basis of foreign body giant cells.

Kruckmann<sup>294</sup> undertook to determine whether or not all giant cells were the same, regardless of the tissue in which they might occur. He compared those in tuberculosis with those found around foreign bodies, about parasites, in sarcomas and in epithelial tumors, and decided that they were not all alike, but that they came from several different sources. He concluded that many of them could be accounted for on a foreign body giant cell basis, and that they were formed about such substances as pigment, glycogen, amyloid and possibly hyalin. He cited Lubarsch's instructive case of a periosteal sarcoma of the forearm, which proved that some of the giant cells could be entirely independent of the essential cells of a tumor. The primary growth contained only spindle cells, the first recurrence was made up of spindle cells and foreign body giant cells together, while at autopsy many of the spindle cells were multinucleated, and comparatively few large giant cells of the type found round a foreign body were present. Kruckmann, in discussing this case, said that, in the last recurrence, two kinds of giant cells were present: those which were related to osteoclasts and belonged to bone, and those which were tumor giant cells and which metastasized to the secondary sites.

Stroebe<sup>340</sup> believed that tumor giant cells were foreign body giant cells which arose from tumor cells, partly by nuclear division and partly by fusion. Klebs<sup>387</sup> not only found multiple mitoses in tumor cells, but such large ones that he called them "giant mitoses." Manz<sup>247</sup> took the stand that the giant cells in sarcomas were of two kinds: one kind arose from the rapid proliferation of true tumor cells and contained many nuclei, the other arose from the degeneration of tumor cells and the fusion of degenerated cells. Rindfleisch<sup>304</sup> believed that the giant cells in bony tumors were osteoclasts released by bony resorption. Malassez<sup>237</sup> traced them to proliferated endothelium, while Boist<sup>47</sup> and Ziegler<sup>389</sup>

thought they had multiple origins Malloiy<sup>241</sup> advanced the explanation that the giant cells in tumors were of at least two types One was a true tumor giant cell originating from tumor cells by multiple mitosis due to rapid growth, and varying with the type of tumor concerned The other was a foreign body giant cell formed by the fusion of endothelial leukocytes The latter cells were not tumor cells, although the tumors which contained them were called "giant cell sarcomas" He said that such sarcomas should be classified according to the nature and type of the essential cell from which they arose, and that the use of the term "giant cell sarcoma" should be discontinued It has been my practice, in instructing students in the subject of giant cell tumors to advise them to disregard the giant cells and study only those cells which unquestionably are tumor cells

*Occurrence of Giant Cells in Tumors of the Bone*—Until recently, the understanding and interpretation of tumors of the bone was in a greatly confused state Since almost all giant cell tumors of bone were classed together, it was difficult to reconcile the great variations in malignancy which were constantly encountered The occurrence of giant cell tumor of the bone in man was reviewed by M B Schmidt,<sup>320</sup> and its occurrence in animals by Casper<sup>67</sup> In early reports, Rustizky<sup>311</sup> and Hansemann<sup>137</sup> appreciated that in myelomas there were two kinds of giant cells the osteoclasts, and the megakaryocytes, or giant nuclear cells Malloiy's<sup>241</sup> article on giant cell tumors threw considerable light on the question, and the reports of Bloodgood<sup>39-41</sup> demonstrated that there were essential differences in so-called giant sarcomas of bone

The present interpretation is largely due to the work of Codman,<sup>68</sup> who established the "Registry of Bone Sarcomas," and to the "Registry Committee of the American College of Surgeons," to which Codman's collection was given Ewing<sup>96a</sup> was closely associated with the work of the registry, but did not accept Codman's classification in its entirety Kolodny<sup>198</sup> restudied the cases and made still another classification My review follows the original classification, but, as it has to do with the tumors only so far as the various types contain giant cells, a particular text is not followed

*Classification of Tumors* 1 *Metastatic Tumors Primary in Tissues Other Than Bone* Any metastatic tumor which destroys bone, whether it is epithelial or mesoblastic in nature, is likely to contain two kinds of giant cells those multinucleated forms which originate from tumor cells, and those which are associated with the resorption of bone, and which have been interpreted either as ordinary foreign body giant cells or as a specific form of giant cell, the osteoclast

2 **Periosteal Fibrosarcoma** This class includes tumors which morphologically are fibrosarcomas or fibroblastomas and which lie next to the external surface of the bone, but do not invade it. The cells are spindle shaped and may be multinucleated, and they may form fibrils. They may also contain foreign body giant cells about areas of necrosis and hemorrhage, or about elastic or collagen fibrils.

3 **Osteogenic Sarcoma or True Bone Sarcoma** This group is believed to come from the cells from which embryonic bone develops, and so may contain fibrous, myxomatous, cartilaginous and bony or osteoid portions as well as completely undifferentiated cells. The tumors may be periosteal, subperiosteal or medullary in origin, and they may tend to form bony trabeculae, may tend to be sclerosed compact masses or may grow rapidly and take on a loose, spongy structure called the telangiectatic form. All variations of fibrous, myxomatous, cartilaginous or osseous cells may be present, or the general structure may tend to differentiate chiefly into a fibrosarcoma, a myxosarcoma, a chondrosarcoma, an osteogenetic sarcoma, an osteoidsarcoma or the rapidly growing undifferentiated cell form. In any of these types may be found true tumor giant cells, respectively of the fibroblastic, myxoblastic, chondroblastic and osteoblastic forms. Such cells may contain large vacuolated or globular single nuclei with one or several nucleoli, and may be hyperchromatic, with or without the figures of nuclear division, or they may be multinucleated having anywhere from two to a dozen or more separate nuclei. The tumor giant cells tend to differentiate, so far as their shape and intercellular substance is concerned, like the cells from which they come. Therefore, the fibroblastic cells are spindle shaped, with more or less spindle shaped nuclei, and often form fibroglia (Mallory<sup>241</sup>) and collagen, and do not tend to shrink away from the surrounding cells on fixation. Myxoblastic cells are probably modified fibroblasts and resemble them save for the serous or gelatinous intercellular substances. The chondroblastic and osteoblastic giant forms differentiate as irregularly round or oval cells, which shrink away more or less from the intercellular substances. The chondroblastic forms are generally embedded in a more or less definite chondromucinous or cartilaginous ground substance. The multinucleated osteoblasts tend to arrange themselves along the borders of osteoid trabeculae with fibrous tissue on the opposite side. They may be interspersed with single cells of the same type, and may occur in single layers or pile up in concentrated masses.

Mallory describes the other type of giant cells, which are larger, contain great numbers of nuclei and tend to retract from the surrounding cells on fixation, as foreign body giant cells formed from fused endothelial leukocytes. Ewing states that giant cells are found in all forms of

osteogenic sarcomas as a result of the overgrowth or fusion of tumor cells, and may be large or small with single or multilobar nuclei. They are found in the walls of the cysts, along the bony sinuses and about extravasated blood. The presence of great numbers of these foreign body giant cells may lead to an erroneous diagnosis of a benign giant cell tumor.

4 **Inflammatory Conditions** Codman placed inflammatory conditions near the center of the list, because exuberant callus and osteogenic sarcomas are similar in their histology, and because such lesions as osteitis fibrosa and bone cysts are interpreted by some pathologists as tumors and by others as inflammatory lesions. Apparently, the only type of giant cell found in these lesions is of the foreign body or osteoclastic variety.

5 **Benign Giant Cell Tumor** This term was suggested by Bloodgood to replace the older one of "giant cell sarcoma," and was accepted by the registry, because a clear tumor of this group has not been found to metastasize. According to Mallory, these tumors are inflammatory, and were wrongly termed "giant cell sarcomas," because the giant cells are not tumor cells but are all foreign body giant cells. Ewing apparently did not wholly agree, because he offered the synonymous name of "osteoclastoma" for the members of this group. Bloodgood showed that this group, from the clinical standpoint, is not of a malignant nature.

6 **Angioma of the Bone** This tumor is usually benign and frequently contains foreign body giant cells in the stroma and about hemorrhagic areas outside the vessel lined spaces.

7 **Ewing's Tumor** Kolodny stated that Ewing's tumor is a characteristic tumor which varies from osteogenic sarcoma and frequently is multiple. The type cell is small and polyhedral, having round, oval or slightly elongated nuclei and scant, clear, stainless cytoplasm. The nucleus stains palely and contains scattered granules of chromaffin. The nuclei are not easily seen. While mitosis may be abundant, true tumor giant cells or multinucleated cells are not found. It often assumes the form of the old perithelial angiosarcoma. Ewing believed that it originates from the perivascular endothelium, and called it an endothelial myeloma.

8 **Myeloma** Myelomas constitute a group of central tumors not producing bone and made up of cells which resemble the cells of the myelocyte series and which are usually multiple. The exact nature of the cells is not known. According to Mallory, they are not myeloblastic, and by exclusion he suggested the possibility of their origin from erythroblasts or megakaryocytes. The cells are of medium size and often compressed into polygonal forms. Some examples resemble plasma cells. These tumors are often associated with bone resorption.

and multiple fractures. Myelomas have also been called plasmocytoma, lymphocytoma, myelocytoma and erythroblastoma. The tumor cells are often multinucleated (Kolodny<sup>198</sup>). It is possible to get several varieties of giant cell forms: (a) the multinucleated tumor cells, (b) the foreign body osteoclastic forms associated with bone resorption and fractures and (c) megakaryocytes, which are present in the bone marrow, the common site of the myelomas.

In addition to the bone tumors included in Codman's classification, there are two other examples which involve bone and other tissues, but which are not characteristic lesions of bone.

(a) *Epulis*. It was formerly taught that the epulis was an unusual form of giant cell sarcoma affecting the jaws, and known not to produce metastases. At present, the epulis is considered variously as being an inflammatory lesion characterized by the presence of foreign body giant cells, as a fibroma, or benign giant cell tumor, or as an osteoclastoma. In any case, it is not malignant, and the contained giant cells are of the foreign body type.

(b) *Xanthoma*. Giant cells are nearly always found in xanthomas and xanthosarcomas. There are two kinds of xanthomas (Lubarsch<sup>227</sup>): those connected with the eyelids, and those found in joints, tendons, bursa and allied places. The term is not a good one, as it refers to the characteristic appearance of the tumor, not to its true nature. Xanthosarcomas include hemangiomas, endotheliomas, sarcomas and even carcinomas. Garriett<sup>118</sup> reported on a study of 196 tumors diagnosed as xanthosarcoma, and stated that foreign body giant cells may or may not be present, and when present are without particular significance so far as prognosis is concerned. When present, they are usually filled with phagocytosed pigment.

There is probably no other group of lesions in which it is so important to be able to interpret the giant cells as it is in the bone tumors. The prognosis may depend on the differentiation of the kinds found.

*Giant Cells in Tumors Other Than Tumors of the Bone*.—Practically all benign tumors undergo degeneration in part or produce dense fibrillar structures which lead to the formation of foreign body giant cells. These cells are practically all large phagocytes and appear to come from wandering phagocytes by fusion, nuclear proliferation or both.

In fibromas, the cells are present about hyalin pigment, collagen and necrotic foci.

In lipomas, giant cells form in foci of necrosis or in deposits of fatty acid crystals. In fibroids, or leiomyomas, they are common in areas of liquefaction, necrosis and calcification. In endotheliomas, they are seen about small extravasations of blood. In dural endotheliomas (the



arachnoid-fibroblastoma of Mallory), foreign body giant cells are common about bits of hyalin which are included in the whorls

In fibrosarcomas, leiomyosarcomas and melanomas, both true tumor cells and foreign body giant cells are likely to be found

Psammoma, like xanthoma, is not a tumor characterized by a specific type of cell, the term is applied to any tumor containing sandlike granules. Similar structures occur in various forms, and are found in carcinomas, in dural endotheliomas and in the dura along the longitudinal sinus of the skull. In the dural growths, the sandlike material is calcified hyalin (Mallory). Psammomas usually contain numbers of giant cells of the foreign body type

Rhabdomyomas and rhabdomyosarcomas contain the most beautiful of all tissue giant cells. Most of them are true tumor cells and are large, irregular embryonic muscle cells. They vary greatly in size and shape, may have single or multiple nuclei, nuclear figures, multiple nucleoli and varying degrees of hyperchromatosis. Those arising from heart muscle usually have each a single nucleus with beaded, radiating striae filling the cytoplasm. In those from striped muscle there are often spheres, rhomboids, ovoids, racket shaped cells and slender ladder-like structures which are prolongations of cells containing crossed striae. Foreign body giant cells may also occur in these tumors, but, as a rule, they may easily be differentiated. If not, they can be specifically stained by several stains, of which Mallory's phosphotungstic-acid-hematoxylin is, perhaps, the best

Ribbert<sup>301</sup> interpreted the muscle giant cells of rhabdomyomas as of congenital origin rather than as metaplastic products, because of their resemblance to embryonic muscle and on account of the occurrence of the tumors in early life and in association with mixed tumors

In 1872, Langhans reported giant cells in malignant lymphoblastomas, which he thought were identical with those of tuberculosis. Askanazy<sup>14</sup> and Paltauf<sup>279</sup> also found them in lymphosarcomas. From the time that Hodgkin<sup>163</sup> described seven clinical cases of bilateral symmetrical enlargement of the glands of the neck, a lively controversy has been waged between the school which classifies the disease as granuloma and those which believe it to be a form of lymphoblastic tumor. Regardless of the reader's convictions in the matter, in both Hodgkin's disease and lymphoblastic tumors two similar types of giant cells are usually found. One of these is characteristic of the growth in both conditions, although much more easily demonstrated in Hodgkin's disease. It is often spoken of as the "Steinberg Cell"<sup>334</sup> or as the "Dorothy Reed Cell"<sup>298</sup>. According to Reed, the cell is a transformation of an epithelioid cell which, in turn, has come from the endothelium lining the lymph sinuses or cover-

ing the reticulum of the germ center. According to Malloiy,<sup>212</sup> it is a lymphoblast. Reed describes it as a large epithelioid type of cell with a vesicular nucleus or with several nuclei, generally of a bean shape, and having prominent nucleoli. The nuclei may be in the periphery or arranged in a central clump. She did not observe mitoses in them. The lymphoblast of Malloiy is the same cell, and often contains numerous typical and atypical mitotic figures. Reed described another type of giant cell with small peripherally arranged nuclei, which she interpreted as Langhans' giant cell. Malloiy also stated that Hodgkin's disease commonly contains foreign body giant cells. Apparently, the two types are found associated constantly in Hodgkin's disease and tumors of the lymphoblast group, but are wholly unrelated so far as origin is concerned.

Foreign body giant cells in chloroma have been described by Billroth,<sup>37</sup> and in Gaucher's disease of the spleen by Waugh and MacIntosh.<sup>385</sup>

Gliomas and gliosarcomas frequently contain two types of giant cells: one is a multinucleated glial cell (Bailey and Cushing<sup>21</sup>), which is specific for glial tumors, the other is not distinguishable from the foreign body giant cell. It most likely originates from phagocytic cells of the blood or vascular tissues, and is of endothelial nature, but, as was mentioned under the discussion of varieties of giant cells, they have been attributed to wandering glial phagocytes of the ameboid class of Alzheimer, and this possibility has not been definitely excluded.

*Epithelial Tumors*—Two kinds of giant cells have been described as occurring in epithelial tumors: those which come from epithelial tumor cells, and those which are foreign body giant cells similar in all respects to foreign body giant cells elsewhere in the body. Krause<sup>202</sup> was one of the first to study giant cells in carcinomas. He found them in the centers of the epithelial pearls and in the margins of epithelial islands in ten of seventy epitheliomas which he reported. He thought they formed through the compression and fusion of tumor cells. Kruckmann<sup>204</sup> found giant cells in sebaceous adenomas, dermoid cysts and epitheliomas, and concluded that they are snared-off bits of tumor epithelium. Oltz<sup>275</sup> found them in the stroma about cancer nests in association with calcium salts, and explained them on a foreign body giant cell basis. Lubarsch<sup>226</sup> stated that foreign body giant cells are common in cancers and are present about areas of cornified epithelium, cell detritus, cholesterol and deposits of calcium. Apparently all of these authors were dealing with foreign body giant cells, though they were not agreed as to their origins. C. Lubarsch<sup>224</sup> reported typical foreign body giant cells in a hypernephroma. They are common in adenomas of the meibomian glands (Weis<sup>374</sup> and Zielonko<sup>390</sup>).

The term "carcinoma gigantocellulare" has sometimes been applied to carcinomas, but it should be reserved for tumors composed of large syncytial masses of tumor cells, and should not be used in connection with carcinomas in which only foreign body giant cells are found. Babes<sup>20</sup> reported a carcinoma of the liver, which was composed of large multinuclear syncytial-like cell masses in which great numbers of mitoses were present. Goldzieher and Makai<sup>123</sup> encountered a large multinuclear cell parenchymatous tumor to which they applied the term "gigantocellulare." Rowen and Malloy<sup>310</sup> reported a similar tumor, and I have seen two others within the last year. Giant epithelial cell tumors sometimes occur in the cervix, breast, esophagus and intestinal tract. Tumors composed of large syncytial epithelial masses have been reported in chordomas by Malloy, and in choriocarcinomas of the uterus and testis by Aschoff,<sup>11</sup> Marchand<sup>252</sup> and others. Cells of the latter types are easily differentiated from foreign body giant cells.

#### CRITICAL CONCLUSIONS

1 The multinuclear giant cells of the body may be divided into two groups: (a) specific tissue cells, which include megakaryocytes, muscle repair cells, epithelial syncytia of parenchymatous and placental origin, and true multinucleated type cells from various tumors, (b) foreign body giant cells, which include the large multinuclear phagocytic cells occurring about pigment, inorganic salts, crystals and foreign bodies, the Langhans cell of tuberculosis, and the similar foreign body cells of syphilis, leprosy and other granulomas, the foreign body giant cells of tumors, and the osteoclasts.

2 The foreign body giant cells either are identical or are all closely related to each other, and probably are all derived from mononuclear phagocytes.

3 The participation in the formation of foreign body giant cells by lymphocytes has not yet been definitely proved, although phagocytosed lymphocytes within them are not uncommonly seen.

4 The question regarding nuclear multiplication and fusion is still unsettled. Fusion has been observed in tissue cultures, and some of the histologic pictures are difficult of interpretation in any other way, but nuclear proliferation also occurs in tissue cultures, and occasionally mitoses have been observed in foreign body giant cells. It is probable that either method of increasing the number of nuclei may occur.

5 The function of foreign body giant cells is undoubtedly one of phagocytosis and defense. It is possible that giant cells may protect tubercle bacilli mechanically for a time, and even distribute them within a limited radius.

6 Foreign body giant cells are so widely distributed in all types of pathologic lesions that when they are encountered in a section, the pathologist should rule out other possibilities before making the diagnosis of tuberculosis

7 The giant cell of tuberculosis is a type of foreign body giant cell, and cannot be differentiated from the giant cells of other granulomas except by the demonstration of tubercle bacilli

8 The diagnosis of giant cell sarcoma should not be applied to a tumor when foreign body giant cells are the only kind of multinucleated cells present. The effort of the pathologist should instead be directed toward interpreting the type of the essential cell composing the new growth

9 The differentiation between foreign body giant cells and true tumor giant cells is usually not difficult if the points already cited are kept in mind

10 The presence of a mitotic figure in a giant cell when found in a new growth usually indicates that the cell which contains it is a true tumor giant cell and that the tumor itself is malignant

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## Notes and News

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**University News, Promotions, Resignations and Appointments** — Frederick R Weedon, formerly of the department of pathology of the University of Chicago, has been appointed pathologist of the Macon Hospital, Macon, Ga

An assistant professorship of pathology in the college of medicine of the University of Tennessee, Memphis, is vacant

John Hays Bailey has been appointed Huesmann fellow at the Riley Hospital for Children of the Indiana University, Indianapolis

At Stanford University, Albert Paul Krueger has been promoted to assistant professor of bacteriology

Eric D'Ath has been made professor of pathology in the University of Otago, New Zealand

Ralph W Webster has been appointed chemist to the coroner's office of Cook County (Chicago) in the place of William D McNally, resigned

Robert L Benson has resigned as head of the department of pathology in the University of Oregon Medical School, Portland, Ore, and Frank R Menne has been appointed in his place Dr Benson will remain connected with the school nominally as clinical professor of pathology

H Douglas Symmers has been appointed general director and Armin V St George assistant director of the hospital laboratories of New York City

Giuseppi Caroma of the Institute of Epidemiology, Naples, is to work for a year on measles and scarlet fever at the Hooper Foundation for Medical Research of the University of California, San Francisco

Robert Hegner, professor of protozoology in Johns Hopkins University, is to serve for one year as visiting professor in the University of the Philippines, Manila

Carl Koller, New York, has received the Kussmaul medal of Heidelberg University for his work in Vienna in 1884 on cocaine as a local anesthetic in ophthalmology

The annual John Scott medal of the city of Philadelphia has been awarded to Herbert M Evans, professor of anatomy in the University of California, for his work on the antisterility vitamin E

Alfred Maurice Wakeman of the Yale Medical School died at the age of 32, on March 2, 1929, at Lagos, Africa, while investigating yellow fever

Maurice Letulle, professor of pathologic anatomy in the Faculte de Paris and a member of the Academie française, died at the age of 76

Erwin Christeller, professor of pathologic anatomy in Berlin, died recently

Eugene Latreille, professor of pathology in the Universite de Montreal, died recently

**Registry of Technicians** —The American Society of Clinical Pathologists has organized a registry for laboratory technicians Certificates are issued to properly qualified persons Schools and laboratories that give courses for training technicians are to be inspected and standardized The registry also will conduct a placement bureau for registered technicians

**Meeting of Association of American Physicians** —The fourth annual meeting of the Association of American Physicians will be held at the Hotel Travmore, Atlantic City, N J, May 7 and 8, 1929

**News of Societies**—At the recent annual meetings in Chicago, the American Association of Pathologists and Bacteriologists elected officers as follows: president, George H. Whipple, vice president, G. R. Callender, treasurer, F. B. Mallory, secretary, Howard T. Karsner, member of the council, E. T. Bell.

The American Association of Immunologists elected the following officers: president, Oswald T. Avery, secretary-treasurer, Arthur F. Coca, and councilor, S. Bayne-Jones.

The International Society of Microbiology will hold an international congress in Paris in September, 1929.

The Seventh International Congress of the History of Medicine will meet in Rome in September, 1930. The president is Dr. Pietro Capparoni, 108 Via Pozzetto, Rome.

The next International Physiological Congress will meet in Boston, August 19-23, 1929, under the presidency of William H. Howell. Walter B. Cannon, Harvard Medical School, has charge of the arrangements.

The next annual meeting of the American Society of Clinical Pathologists convenes in Portland, Ore., July 5, 6 and 8, 1929.

The twenty-second annual meeting of the American and Canadian Section of the International Association of Medical Museums was held in Chicago on March 27. The following officers were elected: president, H. E. Robertson, vice president, G. R. Callender, secretary, Maud E. Abbott.

# Abstracts from Current Literature

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## Experimental Pathology and Pathologic Physiology

### CALCIUM AND PHOSPHOROUS METABOLISM OF EPILEPTIC CHILDREN RECEIVING A KETOGENIC DIET MARTHA NELSON, Am J Dis Child **36** 716, 1928

Determinations were made of the calcium and phosphorus intake and output of three epileptic children receiving a ketogenic diet. In each instance, the output of calcium and phosphorus exceeded the intake. There was a shift of the major excretion from the stool to the urine, the increase of urinary calcium being proportionally greater than the increase of urinary phosphorus. The values for the calcium and phosphorus of the blood during fasting were within normal limits.

AUTHOR'S SUMMARY

### \* THE EFFECT OF THE LEVEL OF OVARIAN ACTIVITY ON THE METABOLISM OF GALACTOSE ALLAN WINTER ROWE and MARY MCGUINESS, Am J Obst & Gynec **16** 687, 1928

Rowe and McGuiness demonstrated that the limits of assimilation of galactose vary with the functional activity of the ovaries. In prepubertal years the average galactose tolerance was 20 Gm. There was a gradual increase with the onset of puberty, and the highest tolerance, 40 Gm, was reached during maturity. When the menses ceased there was a moderate decrease in tolerance, but when the ovaries were removed the tolerance was decreased to the prepubertal level.

A J KOBAK

### ARTIFICIAL PRODUCTION OF STERILITY WITH SPECIAL REFERENCE TO EXPERIMENTAL TEMPORARY STERILITY BIOLOGICALLY INDUCED IN THE FEMALE JULIUS JARCHO, Am J Obst & Gynec **16** 813, 1928

Jarcho adduces experimentally that rabbits can be artificially rendered temporarily sterile by injecting spermatozoa obtained from rabbits, guinea-pigs and sheep. The rabbits were divided into three series: those injected with (1) live spermatozoa washed and unwashed, (2) spermatozoa killed by formalin, and (3) spermatozoa destroyed and disintegrated by grinding in a mortar containing sea sand. From the latter, emulsions were made with sodium chloride or alcohol. The spermatozoa were also disintegrated by sodium hydroxide which was afterward neutralized with normal hydrochloric acid. The solutions of emulsified spermatozoa were first passed through a Berkefeld filter before using. The spermatozoa in all series were injected hypodermically or intramuscularly in doses of 30,000,000 per cubic centimeter in the series in which the sperms were intact. The behavior of the rabbits thus inoculated was normal. Spermatotoxicity of the serum was discussed but was found to be inconstant. It was suggested that the toxic agent was in the vaginal secretions and the spermatozoa were probably destroyed in the vagina after normal copulation.

A J KOBAK

### PHYSICAL DEVELOPMENT AND THE EXCRETION OF CREATINE AND CREATININE BY WOMEN P HODGSON and H B LEWIS, Am J Physiol **87** 288, 1928

In a number of women with unusual physical development—professional students in courses in physical education—creatinine coefficients of the same order as those of men were found. The excretion of creatine was found with a frequency similar to that usual in women, indicating that the creatinuria of the female sex is probably not related to differences in muscular development in men and women.

H E EGGERS

THE DEVELOPMENT OF SECONDARY SEX CHARACTERS IN CAPONS BY INJECTIONS OF EXTRACTS OF BULL TESTES L C MCGEE, M JUHN and L V DOMM, *Am J Physiol* **87** 406, 1928

The injection of a benzene-soluble lipin fraction obtained from bulls' testicles caused in capons a growth of comb, wattles and ear lobes. The amounts injected were from 150 to 500 Gm of fresh testicular material. Individual variation was observed, but the reaction was sufficiently constant to serve as a roughly quantitative method of assay of the lipin preparation. Partial purification of the material was effected by fractional precipitation by methyl alcohol, ethyl alcohol and acetone, or by extraction with liquid ammonia. The activity of the material was only partly affected by boiling with alcoholic sodium hydroxide for nine hours, but was lost completely after boiling for eighteen hours.

H E EGGERS

THE EFFECTS OF LIPOID EXTRACTS OF BULL TESTES ON CASTRATED GUINEA-PIGS C R MOORE and L C MCGEE, *Am J Physiol* **87** 436, 1928

Using benzene-soluble lipid extracts of bull testes, it was found that the injection of these into castrated guinea-pigs gave effects similar to those of the intact living testicle. As a measure of this effectiveness, the rate of persistence of living spermatozoa in the epididymis was selected. In the absence of a testicular hormone, these persist for twenty-three days. In the animals receiving the injections, they persisted for from thirty-five to fifty-four days, while their persistence in uncastrated normal animals is sixty-five days.

H E EGGERS

DISTRIBUTION OF TESTICULAR COMB GROWTH STIMULATING PRINCIPLE IN TISSUES T F GALLAGHER, *Am J Physiol* **87** 447, 1928

A study of the possible sources of the lipoidal hormone of bull testis showed that it was absent in all other tissues except the epididymis, where it was present in lesser amount than in the testis. It was not found in whole beef ovary.

H E EGGERS

AN IMPROVED METHOD FOR THE DETERMINATION OF CARDIAC OUTPUT IN MAN BY MEANS OF ETHYL IODIDE I STARR, JR and C J GAMBLE, *Am J Physiol* **87** 450, 1928

The authors found it impossible to estimate correctly the ethyl iodide content of arterial blood from the content of this substance in the alveolar air, and of venous blood by the content in rebreathed air. They report a series of experiments by which a method is developed for the determination of the rate of the blood flow through the lungs, which requires no active cooperation of the subject.

H E EGGERS

THE RESPIRATORY QUOTIENT AND BASAL METABOLIC RATE FOLLOWING REMOVAL OF THE LIVER AND INJECTION OF GLUCOSE F C MANN and W M BOOTHBY, *Am J Physiol* **87** 486, 1928

Using trained dogs, a series of observations of gaseous metabolism was made before and after removal of the liver and before and after the injection of dextrose. While the respiratory quotient increased immediately after removal of the liver, the total production of heat was not directly affected by the total loss of hepatic tissue, dextrose had a greater specific dynamic action in dehepatized than in normal animals.

H E EGGERS

THE EFFECT OF REMOVAL OF THE LIVER ON THE SPECIFIC DYNAMIC ACTION OF AMINO-ACIDS ADMINISTERED INTRAVENOUSLY C M WILHELMJ, J L BOLLMAN and F C MANN, *Am J Physiol* **87** 497, 1928

Following the two operations (reverse Eck fistula with ligation of the vena cava and later ligation of the portal vein) preceding removal of the liver in

dogs, there was found to be no alteration of the specific dynamic action of amino-acids injected intravenously. Following removal of the liver there was no evident change of the consumption of oxygen, but the respiratory quotient showed spontaneous and persistent elevation. The intravenous injection of amino-acids into these animals failed to produce an increased consumption of oxygen, but further elevated the respiratory quotient. A specific dynamic effect of the amino-acids failed in the same way with the blood sugar content within normal limits. The experiments indicate that the specific dynamic action of the amino-acids is not the result of direct stimulation by the presence of unchanged amino-acids within the tissues.

H E EGGERS

PHYSIOLOGICAL ACTIVITY AND THE MANOILOV REACTION O RIDDLE and  
W H REINHART, *Am J Physiol* **87** 517, 1928

In a study of the Manoilov reaction (the modification of the oxidation of dahlia by body fluids), it was found that the test was really an expression of the metabolic activity of the part represented by the fluid, and that to the extent that it serves as a sex-reaction, the test is based on the relation of metabolism to sex.

H E EGGERS

PRODUCTION OF RENAL INJURY IN THE WHITE RAT BY THE PROTEIN OF THE  
DIET L H NEWBURGH and A C CURTIS, *Arch Int Med* **42** 801, 1928

Young white rats were given adequate diets containing an excess of proteins for varying lengths of time to more than 500 days. Evidence of injury of the kidneys was found in the urinary casts and albumin, and in histologic sections. Excess of casein caused but little nephropathy, even in amounts of 75 per cent given for more than a year. Beef muscle proteins in amounts greater than 31 per cent of the diet gave casts, albumin and degenerative changes of the tubules and glomeruli with fibrosis. Seventy-five per cent of beef liver caused marked granulation of the kidneys in 300 days. It is believed that the amino-acid make-up of a protein determines its nephrotoxic action.

HAMILTON R FISHBACK

EXPERIMENTAL UREMIA M H STREICHER, *Arch Int Med* **42** 835, 1928

A ten to twenty per cent solution of urea was injected intravenously into dogs, at the rate of 200 cc daily for three days. In about 40 per cent of the dogs a picture resembling uremic coma was produced after injecting 200 per cent of urea solution, while practically all the animals became comatose after the second or third injection of 200 cc. Urea in the blood increased to 700 mg after the third injection. There was an increase in blood calcium and a decrease in potassium, so that the potassium-calcium ratio fell below one. The carbon dioxide was constantly decreased as in human uremic acidosis, and the blood pressure rose as high as 220 mm of mercury. The intestines showed marked hyperemia but no ulceration.

HAMILTON R FISHBACK

THE UREA TOLERANCE TEST S E KING, *Arch Int Med* **42** 877, 1928

Kidney function was studied by repeated estimation of the blood urea after giving by mouth 1 Gm of urea for each 10 pounds (4535 Gm) of body weight. Standard conditions were adopted as to fluid and food intake and rest in bed. In all normal subjects the blood urea had dropped to within 2 mg of the rest level after fourteen hours. In a series of cases with definite renal impairment the average elevation of the blood urea nitrogen in two hours was 15.9 mg, as compared with a normal amount of 10.5 mg. After fourteen hours the blood urea nitrogen averaged 10.3 mg above the rest level. In over half these cases the urine was in excess of the 750 cc set as a maximum normal amount.

HAMILTON R FISHBACK



THE EFFECT OF PARATHYROID EXTRACT ON EDEMA A CANTAROW and B GORDON, Arch Int Med **42** 939, 1928

The blister method for studying the permeability of capillaries and the intra-dermal test with salt solution were carried out on patients with tuberculosis, nephritis and cardiac conditions. Variation of the calcium content of the blood was effected by the injection of parathyroid extract. The appearance of the blister was delayed and the rate of accumulation of blister fluid was decreased after the administration of parathyroid extract. The permeability ratio gave contradictory results in the same cases. It is considered that the chief factor in the production of inflammatory edema is increased permeability of the walls of the capillaries. The duration of the wheal after the injection of salt solution into the skin of patients with nephritis and cardiac conditions was lengthened in every case after the injection of parathyroid extract. The increase of available calcium seemed to lessen the capacity of tissue colloids for hydration, probably through the replacement of sodium ions by calcium.

HAMILTON R FISHBACK

STUDIES ON THE METABOLISM OF ESKIMOS P HEINBECKER, J Biol Chem **80** 461, 1928

A brief account of the diet of Polar and Baffin Island Eskimos is given. By means of glucose tolerance curves it is shown that these people have a high tolerance for carbohydrate. Following a period of fasting this tolerance is markedly decreased. The non-protein nitrogen of the blood of Eskimos is similar to that of other races. The results indicate no retention of nitrogenous products in the blood from the habitual high protein diets. Eskimos show a remarkable power to oxidize fats completely, as evidenced by the small amount of acetone bodies excreted in the urine in fasting. The basal metabolism of Eskimos is considerably higher than that of persons living in temperate zones. During fasting the respiratory quotient falls to a level which may be interpreted as indicating a conversion of fat into carbohydrate.

AUTHOR'S SUMMARY

THE EFFECT OF SCURVY-PRODUCING DIETS AND TYRAMINE ON THE BLOOD OF GUINEA-PIGS M T HANKE and K K KOESSLER, J Biol Chem **80** 499, 1928

Tyramine injected subcutaneously into guinea-pigs does not produce nor lead to anemia in well fed guinea-pigs or in animals that are fed deficient diets. There is no evidence, in these experiments, that, in guinea-pigs, a diet deficient in vitamin A is conducive to anemia nor to the production of abnormal erythrocytes. A diet consisting exclusively of autoclaved soy beans and minerals rapidly leads to scurvy symptoms and death. In such animals an abnormal red blood picture is invariably obtained. There is present a marked polychromatophilia, anisocytosis, and poikilocytosis. The smear may contain a high percentage of nucleated red cells. Reticulocytes may be present in quantities up to 25 per cent. The abnormal red blood picture may, occasionally, be associated with an anemia.

AUTHORS' SUMMARY

BLOOD SUGAR AND RESPIRATORY METABOLISM TIME CURVES OF NORMAL INDIVIDUALS, FOLLOWING SIMULTANEOUSLY ADMINISTERED GLUCOSE AND INSULIN I M RABINOWITCH and E V BAZIN, J Biol Chem **80** 723, 1928

The simultaneous administration of insulin and carbohydrate to normal (non-diabetic) persons does not result in an increase in the rate of oxygen consumption, carbon dioxide production or heat production. The normal rates are, on the contrary, significantly depressed, indicating that "insulin not only does not enhance oxidation of sugar in the normal individual, but in some as yet unexplained way interferes with the normal mechanism."

ARTHUR LOCKE

EXPERIMENTAL EXTRACORPOREAL THROMBOSIS WALTER R JOHNSON, TAKUJI SHIONOYA and LEONARD G ROWNTREE, J Exper Med 48 871, 1928

The processes of blood coagulation and of thrombosis in the extracorporeal loop are definitely delayed in experimental obstructive jaundice and in animals that have received intravenous injections of bile salts. No attempt is made to explain the changes found in jaundice on the basis of the increased levels of bile acids in the blood although these experiments would indicate that such a possibility has not been ruled out.

AUTHORS' SUMMARY

BLACKTONGUE PREVENTIVE IN YEAST JOSEPH GOLDBERGER, G A WHEELER, R D LILLIE and L M ROGERS, Pub Health Rep 43 657, 1928

The blacktongue-producing potency of a basic experimental diet and of three modifications was tested 33 times in 31 dogs with the production of 33 separate attacks of blacktongue. Only one of these attacks developed at the end of a period longer than sixty-one days.

Experimental blacktongue is due to a dietary deficiency which is capable of being corrected by some substance in yeast.

This blacktongue preventive in yeast is inactivated or destroyed by heat sufficient to char the yeast, retains its preventive potency in large measure, if not entirely, after heating in the steam autoclave at a pressure of 15 pounds (68 Kg) for seven and one-half hours, and is adsorbed from an acidulated aqueous extract of either dried yeast or of yeast first autoclaved at a pressure of 15 (68 Kg) pounds for two and one-half hours by English fuller's earth. It cannot be identified with any of the older well recognized dietary essentials, but is believed to be identical with the thermostable substance of Smith and Hendrick.

The blacktongue preventive and the pellagra preventive are both present in yeast. Taken in conjunction with certain other evidence pointing to the fundamental identity of blacktongue and pellagra, this association strengthens the probability that the blacktongue preventive and the pellagra preventive, or vitamin P-P, are identical.

AUTHORS' SUMMARY

ORGANOTAXIS G D BELONOVSKY and A A MILLER, Ann de l'Inst Pasteur 42 712, 1928

Organ emulsions were prepared from ether killed mice, rabbits and guinea-pigs by aseptic removal, washing, grinding with sand and suspension in saline. These were mixed with iron salts, dyes or sodium salicylate and incubated for twelve hours in an oven. The doses that were lethal to mice were determined in chemical studies of the distribution of the foregoing substances. The distribution was definitely influenced by the injection of the organ emulsion with a chemical substance as compared with the injection of the chemical substance alone. Trypan blue emulsified with rat cancerous tumor was also used on cancerous rats. The authors conclude: "The injection of animals with colloidal dyes and with some chemical substances mixed with emulsions of different organs produces an elective concentration of the chemical introduced in the organ an emulsion of which was used, one can assume a double mechanism, positive chemotaxis of the apparent cells (organotaxis), and intensified absorption of the materials by the cells of the organ finding itself in a state of irritation due to the action of specific cytotoxins." Color plates are included.

M S MARSHALL

ANEMIA OF THE TONGUE AN IMPORTANT EARLY SYMPTOM OF ARTERIAL AIR EMBOLISM G LIEBERMEISTER, Klin Wchnschr 8 21, 1929

Air embolism of the tongue with resultant segmental or complete anemia is an early manifestation of arterial air embolism and generally precedes the more severe manifestations. When observed during the collapse of a lung by gas it is an important symptom.

EDWIN F HIRSCH

REGULATION OF BLOOD SUGAR, FAT AND CARBOHYDRATE METABOLISM F  
DEPISCH and R HASENOHRL, *Klin Wchnschr* 9 202, 1929

The administration of fat (50 Gm) has no effect on the blood sugar curve in normal persons. Simultaneous estimations of the capillary and venous blood disclose no differences from which may be concluded that a diet of fat does not cause a secretion of insulin. In the patient with diabetes, the blood sugar curve after a diet of fat is parallel with the hunger curve, and there is no difference between the capillary and venous blood. Injection of epinephrine causes in the normal subject, three hours after a diet of fat, a faster and higher increase of blood sugar than the experiment on hunger control which reveals an abnormal mobilization of liver glycogen by the fat. A diet of fat diminishes the effect of the exogenous administered as well as the endogenous insulin.

AUTHORS' SUMMARY

THE PATHOLOGIC PHYSIOLOGY OF THE ENDEMIC GOITER F DE QUERVAIN,  
Transactions of the International Conference on Goiter, Bern, Switzerland,  
Aug 24-26, 1927 Edited by Hans Huber, Bern, 1928

The pathologic physiology of endemic goiter should cover all the morbid manifestations of the goiter noxa in the human body, and not only the gross anatomic changes in the thyroid gland to which the name of goiter is given. The goiter noxa can affect the structure and functions of the organism (a) indirectly, by injuring the genital glands of parents and by functional inefficiency of the maternal organism, (b) by direct action on the tissues of the body, (c) by injuring the thyroid gland either directly or by functional overwork, and (d) by injuring the other endocrine glands, either directly or as a result of injury to the thyroid gland.

Taking clinical and experimental facts as a basis, endemic goiters may be divided into (a) euthyroid goiters with intermediate stages toward hyperthyroidism and hypothyroidism, (b) hyperthyroid goiters, "struma basedowifcata," in various forms, principally that produced by iodine, and (c) hypothyroid forms including endemic cretinism in one of its clinical aspects.

In endemic cretinism the following types are to be distinguished (a) cretinism without goiter, always accompanied by atrophy of the gland and impairment of growth, and (b) cretinism with goiter, with various degrees of atrophy of the rest of thyroid tissue and varying functional capacity of the goitrous tissue. The striking disparity in the clinical manifestations of the two groups of cretinism may be accounted for by (a) hereditary factors, (b) variations in the earliness and rapidity of onset of injury to the thyroid gland, (c) qualitative modifications of the secretion (relative and, perhaps, absolute dysthyroidism), (d) primary or secondary involvement of other endocrine glands, and (e) direct, extrathyroidal action of the goitrous noxa.

The iodine content of the blood is maintained at a constant level within the limits of seasonal variations. The iodine content is determined by the degree of functional activity of the thyroid gland. For a given intake of iodine, it is at its highest in Graves' disease, is approximately normal in the case of euthyroid goiter and is abnormally low in cretinism with or without goiter.

AUTHOR'S SUMMARY

ETIOLOGY AND EPIDEMIOLOGY OF ENDEMIC GOITER R McCARRISON, Trans-  
actions of the International Conference on Goiter, Bern, Switzerland,  
Aug 24-26, 1927 Edited by Hans Huber, Bern, 1928

Three types of simple goiter are described. The first is the classic type occurring in mountainous regions and variously named parenchymatous goiter, adenoparenchymatous goiter, simple hyperplastic goiter and chronic hypertrophic goiter. The second is the diffuse colloid goiter, and the third is called the lymphadenoid goiter. The goiter-producing influences known are deficiencies and excesses in food, polluted water supplies, gastro-intestinal infection and insanitary conditions.

of life It is impossible to assert that all cases of goiter originate from the same cause We now know that goiter is a generic term which includes a variety of diseases of diverse etiology Future research may further subdivide the simple goiters, clinically, pathologically and etiologically But meanwhile large numbers of them may be prevented by attention to the fundamental principles of nutrition and of personal and social hygiene

## AUTHOR'S SUMMARY

ETIOLOGY AND EPIDEMIOLOGY OF ENDEMIC GOITER B GALLI-VALERIO, Transactions of the International Conference on Goiter, Bern, Switzerland, Aug 24-26, 1927 Edited by Hans Huber, Bern, 1928

The causation of endemic goiter is not yet fully understood

Of the numerous theories that which establishes drinking water as the cause of goiter is at once the oldest and the best supported by fact and experiment, as shown by the following observations (a) the detection of contamination of the drinking water in all endemic districts, (b) the abatement and disappearance of the endemic under improved conditions of the supply of drinking water, and (c) the appearance of goiter in animals that have been watered from sources in endemic districts or with artificially contaminated water

The noxa of goiter in drinking water is either a specific substance or a specific germ or group of germs, especially of the intestinal flora, which produce toxic substances that act on the thyroid gland As a consequence, disinfection of the bowel is beneficial and a regimen favoring constipation is the reverse

The theory that establishes drinking water as a cause does not exclude the possibility of other vehicles for spreading the endemic In like fashion, cholera, enteric fever and dysentery, in all of which the drinking water is usually at fault, can equally be conveyed by milk, vegetables, direct infection, etc

Apart from water supply inbreeding is a predisposing factor in cretinism and deafmutism

The theory of the causation of goiter by deficiency of iodine cannot be accepted (a) because even where iodine is present in excess (sea-coast and sea) goiter may develop, and (b) because deficiency of iodine causes atrophy, not hypertrophy, of the thyroid gland

Iodine is merely, in some way, an antidote to goiter, as is quinine to malaria The theory that goiter is caused by drinking water has much to recommend it from the side of prophylaxis as it leads to an improvement of the water supply

## AUTHOR'S SUMMARY

THE GEOGRAPHICAL DISTRIBUTION OF ENDEMIC GOITER E BIRCHER, Transactions of the International Conference on Goiter, Bern, Switzerland, Aug 24-26, 1927 Edited by Hans Huber, Bern, 1928

Endemic goiter is part of a complex pathologic manifestation characterized by a distinct geographic distribution In the countries where it prevails it can present temporary variations of different intensity, as increase or diminution In the countries where endemic goiter prevails, the goiter varies in its character Endemic goiters of different countries cannot be compared with each other, as the difference is both quantitative and qualitative The histologic structure is also of pronounced variety The etiologic factor of goiter and the conditions which favor its prevalence are of a varied nature One cannot admit a uniform etiologic factor

## AUTHOR'S SUMMARY

THE FORMATION OF BILE LUDWIG ASCHOFF, *Acta path et microbiol Scandinav* 5 338, 1928

This is a lecture in which present knowledge of the formation of bile and its disturbances are discussed The following scheme is presented

Hyperfunctional types Icterus in pernicious anemia, familial icterus and icterus neonatorum

Retentional type icterus in dogs deprived of the liver  
 Retentional and resorptional type icterus in starvation  
 Hyperfunctional, retentional and resorptional types Catarrhal icterus, infectious icterus (Weil's disease) and toxic septic icterus  
 Resorptional type mechanical icterus  
 Aschoff uses the word dyscholia to signify disturbances in the formation and elimination of bile-forming substances  
 A long list of references is given

## Pathologic Anatomy

COMMUNICATING HYDROCEPHALUS JOSEPH H GLOBUS, *Am J Dis Child* **36**: 680, 1928

In two of the five cases presented in this report there was almost complete obliteration of the subarachnoid channels. Because of the embryonal structure of the pia mater and the absence of evidence of inflammatory changes, it was assumed that the defect was on a developmental basis.

The third case differed from the first two in that the hydrocephalus was less marked and of slower development. This picture results from the fact that a small number of the channels had opened.

The fourth and fifth cases illustrate respectively the type of hydrocephalus due to obliteration of the subarachnoid channels by infection, and the type resulting from organization of traumatic hemorrhagic exudate.

Dandy and Weed, although disagreeing as to the mechanism, are both of the opinion that a patent subarachnoid space is essential for the normal distribution of cerebrospinal fluid. When there is an obstruction of the channels without blockage of the flow of spinal fluid between the ventricular cavities, the result is communicating hydrocephalus.

The dye test helps to differentiate the obstructive type from the communicating type.

H E LANDT

BLOOD IN THE STOOLS OF THE NEW-BORN BASNET E BONAR, *Am J Dis Child* **36** 725, 1928

The benzidine test for occult blood was found positive in 29.38 per cent of 1,518 stools of 109 new-born. Occult blood is found too frequently in the stools of the new-born to ascribe its cause to the usual sources. Neither should it be considered physiologic. Certain observations seem to warrant the assumption that the bleeding is due to an intense hyperemia set up in the upper portion of the small intestine by products of digestion, by the primary bacterial invasion, or by both. More attention should be given the so-called initial diarrhea of the new-born which appears to be another manifestation of the irritability of the bowel which occurs in early days of life.

AUTHOR'S SUMMARY

SICKLE CELL ANEMIA MARTHA WOLSTEIN and KATHERINE V KREIDEL, *Am J Dis Child* **36** 998, 1928

In New York, sickle cell anemia is as common as it is in cities of the South and West. In a series of fifteen negro children whose blood showed sickle cells, twelve were in the active phase and three were in the latest phase. In three of the active cases, the patients died of the anemia without other anatomic cause for death. All showed fatty degeneration of the myocardium and liver, distention of the sinuses of the spleen with sickle cells, phagocytosis of the sickle cells by Kupffer cells in the liver and iron pigment in the spleen, liver and kidneys. In two latent cases the patients died of tuberculosis, and in one the patient died of pneumococcus meningitis. Syphilis was present in one child of the series.

AUTHORS' SUMMARY

HEART-BLOCK DUE TO PRIMARY LYMPHANGIO-ENDOTHELIOMA OF 'ATRIO-VENTRICULAR NODE' PUTNAM C LLOYD, Bull Johns Hopkins Hosp 44 149, 1929

A case is described in which a lymphangio-endothelioma had invaded the atrio-ventricular node and the bundle of His, and caused a partial heart-block, terminating in sudden death

AUTHOR'S SUMMARY

THE PHAGOCYTOSIS OF MELANIN BY THE RETICULO-ENDOTHELIAL CELLS IN A CASE OF MELANOBLASTOMA C V WELLER, Warthin Ann, 1927, pp 547-557

The occurrence of melanin in the reticulo-endothelial cells situated near, but apart from, an area of melanoblastoma is common. The presence of melanin in organs and tissues distant from those in which the melanoblastomatous neoplasms occurred has been an infrequent observation, Weller describes such a case. The primary growth was a melanoblastoma of the left eye, which had been enucleated two years before death occurred. The liver showed multiple nodular deeply pigmented metastases. Multiple pigmented metastases were likewise found in the cranium, ribs, sternum and vertebrae. The suprapancreatic, mesenteric, retroperitoneal, bronchial and mediastinal lymph nodes were larger than normal and of a brownish-black color. Small pigmented areas were seen in the suprarenals and in the renal cortex, these had the gross appearance of metastases.

Microscopic studies of the non-neoplastic areas of the liver revealed that melanin was found in granules and dense clumps in the reticulo-endothelial cells. Many of the reticulo-endothelial cells of the leptomeninges contained melanin. In the spleen, even though there were no neoplasm cells, there was well marked melanin deposition in the reticulo-endothelial cells. The lymph nodes revealed an abundance of pigment confined to the reticulo-endothelial cells, entirely like that found in the neoplastic areas of the liver, the lymph nodes showed no metastases of neoplasm cells. Similar phagocytosis of melanin in the absence of neoplasm cells was observed in the suprarenals, gastro-intestinal tract, bone marrow and kidneys. Careful microchemical studies were carried out in order to establish the identity of the pigment.

Weller considers that the distribution and morphology of this pigment can best be explained by the assumption that groups of reticulo-endothelial cells exercise an active selective phagocytosis of the precursors of melanin and that through enzymatic or other intracellular activity melanin is elaborated within the cells. Weller suggests that this mechanism may explain the presence of chromatophores in the meninges of normal persons, particularly of the negro race.

WALTER M. SIMPSON

CRANIOSYNOSTOSIS (OXYCEPHALY AND RELATED DISORDERS) H K FABER, Warthin Ann, 1927, pp 585-600

Faber includes as varieties under the generic term "craniosynostosis" such cranial deformities as oxycephaly (steep-skull), turriccephaly (tower-skull), scaphocephaly, trigonocephaly and phagiocephaly. All have their origin in pathologic synostosis of two or more bones of the calvarium, and are associated in a certain proportion of cases with deformities resulting from synostosis or fusion of adjoining bones in other parts of the body. The anterior and superior portions of the skull (coronal and sagittal sutures) are most frequently involved.

The malformations are conditioned by two factors, first, interference with normal expansion and, second, compensatory overexpansion of unsynostosed regions to accommodate the growing brain. The mechanisms of the development of these deformities are discussed in detail.

The instances of craniosynostotic deformities in more than one generation of a given family are exceptional. More common are examples of their appearance in more than one member of the same generation.

The distinguishing feature in the diagnosis is that the cranial cavity, while deformed, is of normal volume. Visual defects are common and greatly influence the prognosis.

WALTER M. SIMPSON

DIVISION OF CELLS UNDER VARYING TENSIONS OF CARBON DIOXIDE J. C. MOTTRAM, *Brit J Exper Path* 9 240, 1928

Mitoses of normal cells cultivated in vitro occur most abundantly at a carbon dioxide tension approximating that of normal tissues. Under high tensions, abnormal mitoses occur in which there is an irregular migration of the chromatin to the centrosomes.

PEARL ZEEK

VERTEBRAL HYDATID CYST F. DLVE, *Ann d'anat path* 5 84, 1928

Deve affirms that there is no such thing as hydatid cyst of the vertebrae. Experimental and clinical observations led him to the conclusion that the parasite invades this structure in the form of a diffuse osseous microvesicular infiltration. He could never find a regular capsule surrounding the univesicular or multivesicular echinococcus parasite. He therefore recommends to replace the expression of older observers "hydatid cyst" by the term "vertebral echinococcosis." He further states that the disease begins as a milary multilocular lesion and the spongy bony tissue appears to be infiltrated by multiple minute vesicles, which advance by continuity without causing any osteomyelotic reaction. Likewise, the presence of echinococcus in the spinal canal is in all probability of exogenous osseous origin.

B. M. FRIED

NODULAR PERIARTERITIS R. DEBRE, R. LEROUX, P. GAUTHIER-VILLARS and LELONG, *Ann d'anat path* 5 757, 1928

With the naked eye the lesions are seen as milary nodules distributed along blood vessels. With the microscope the entire blood vessel appears to be involved. The intima is thickened and edematous, in the media both elastic membranes show dissociation and often complete destruction. The adventitia is infiltrated with polymorphonuclear leukocytes which also surround the vessel, the vascular lumen is narrowed, irregular and occasionally completely obliterated. However, the microscopic characteristics of the lesion depend on the stage or severity of the disease. The vascular lesions are accompanied by degeneration of the peripheral nerves, by hemorrhages in the brain and in the gastro-intestinal tract, and also by marked lesions in the kidneys. In order of frequency the coronaries, the renal and the hepatic vessels are the more commonly involved, then go the mesenteric, the gastric, intestinal, splenic, pancreatic, etc.

The clinical picture is extremely variable, pointing to a polyneuritis, cardiac insufficiency or to a disease of the peritoneum. The duration of the disease varies from a few days to two years. It is not necessarily fatal. The majority of authors believe it to be caused by a micro-organism. It has been found also in some animals as the pig, the calf and the dog. The authors report a personal observation, discuss the cases from the literature and also give a good bibliography on the subject.

B. M. FRIED

A MIXED EPITHELIOMA OF THE KIDNEY P. MASSON and C. SIMARD, *Ann d'anat path* 5 825, 1928

The case reported by Masson and Simard concerned an epithelioma of the kidney which had two different structures, in one place it resembled tumors originating in the renal pelvis, in the other it looked like carcinoma of the convoluted tubules. Both varieties spread toward and invaded the renal parenchyma. The authors discuss the possibility of this tumor being a primary "double" cancer of the kidney. They are inclined to the belief that both varieties of the neoplasm

originated in the renal excreting epithelium. The complexity of its structure is in all probability being due to the evolutionary potentialities of the excreting epithelium which is capable of giving rise to tumors resembling those of the convoluted tubules

B M FRIED

**NODULAR SCLEROSIS ACCOMPANIED BY A PULMONARY PANARTERITIS IN SYPHILIS OF THE LUNG** H DARRE and G ALBOT, *Ann d'anat path* **5** 861, 1928

Syphilis of the lung may take different aspects: a peribronchial sclerosis or a nodular disseminated fibrosis confined to the perilobular, perialveolar and inter-alveolar tissues associated with a pulmonary panarteritis. There may be no lesions of the bronchi. In instances in which the disease is predominantly confined to the arteries, the pathologic modification resembles those found in the liver, kidneys and other organs. From a clinical standpoint the symptoms are those of cardiac insufficiency

B M FRIED

**MUCOUS SECRETION AND MUCOUS CYSTS IN ADENOCARCINOMA OF THE CORPUS UTERI** ISBRUCH, *Arch Gynak* **135** 102, 1928

By differentiation of the malignant cells, two types of cysts are formed, one containing true mucus taking a mucicarmine stain, and the other containing a homogeneous substance representing a different type of secretion. Isbruch noted that the epithelial cells of the mucous cysts were somewhat higher than those of the other cysts

A J KOBAK

**MORPHOLOGY OF WHITE BLOOD CELLS IN ENTERAL SENSITIZATION AND ANAPHYLAXIS** R GAWRILOW, *Virchows Arch f path Anat* **265** 583, 1927

No definite change in the blood picture was found in rabbits during feedings of egg white or yolk. Relatively often a moderate leukocytosis occurred, with increase in lymphocytes, and without characteristic changes in the other cells. During the following latent period, the white cells were normal or remained slightly increased. Intravenous injections of the same protein were made from fourteen to eighteen days later. In the case of egg white, leukopenia with reduction in eosinophils and increase in lymphocytes occurred at first, and was sometimes followed by leukocytosis with reduced lymphocytes. With egg yolk, there was also a transitory leukopenia, with subsequent leukocytosis, but the reaction to this protein was less marked

B R LOVETT

**THE SECONDARY NODULES IN LYMPH NODES** W ROTTER, *Virchows Arch f path Anat* **265** 596, 1927

Rotter distinguishes five types of nodules in lymph nodes: solid or resting, epithelioid, reticular, lymphoplasmic and necrotic. If these bodies are to be regarded as centers for immunity reactions instead of as germinal centers, their derivation should be from the reticulo-endothelial system. The epithelioid nodules apparently develop from the cells of the blood vessel walls. The nodules then take on a reticular structure, in which the large, free cells, lymphoblasts, develop, probably from the fixed tissue cells. The author believes that the small lymphocytes do not differentiate farther, but that the damaged ones are destroyed in the central space of the nodules, where remains of their nuclei may be found. He formulates the theory that the secondary nodules arise as a reaction principally to hematogenous irritation, the speed and form of the reaction being largely determined by the degree of sensitization of the organism to the irritant. Lymphogenous irritation may also lead to the formation of these centers. He therefore regards them as reaction centers of immunologic significance, but agrees that during retrogression of the lymphoplasmic nodules to the resting stage, they act as germinal centers for the new formation of lymphocytes

B R LOVETT



AMYLOID IN A TUMOR OF THE CERVICAL LYMPH NODES K v GUSNAR, Virchows Arch f path Anat **265** 617, 1927

A local deposit of a homogenous substance was found in a metastatic carcinoma of the cervical lymph nodes. This substance gave the color reactions characteristic for amyloid through most of its extent. Similar masses were also found in the newly developed cells, evidently a hyaline precursor of the amyloid. A sharp distinction between amyloid and hyaline substance cannot always be established.

ADENOMA OF THE FALLOPIAN TUBE A PRILSFL, Virchows Arch f path Anat **265** 630, 1927

In an operation on a woman, aged 30, cherry-sized nodules resembling adenomyomas were found on the uterine portions of both tubes. Histologic examination of one of them showed a fibro-epithelial new-growth, with glandular structures surrounded by cellular tissue. Most remarkable was the presence of numberless islands of pavement epithelium mixed with the cylindrical epithelium of the glands. Pavement epithelium has not, to the author's knowledge, been described in the tubes before, although it is sometimes found in the uterus. Priesel regards these nodules as due to a developmental anomaly, and not to an inflammatory process, partly on account of the presence of the two types of epithelium. The tumors were apparently benign.

B R LOVETT

CONGENITAL LIPOMA OF THE FEMORAL VEIN J GANGLER, Virchows Arch f path Anat **265** 643, 1927

A lipoma the size of an orange was removed from the femoral vein of a girl, 18 months of age. The vein ran through a groove in the mass, which was surrounded by a fibrous capsule everywhere except where there was contact with the vein. The point of origin appeared to be the adventitia of the vein. Since this tissue does not normally contain fat cells, the development of a lipoma from it is evidence for the theory of embryonic displacement of tissue rests as a cause of tumor development.

B R LOVETT

HISTOLOGY OF NEURINOMAS F NESTMANN, Virchows Arch f path Anat **265** 646, 1927

Verocay distinguished neurinomas from neuromas by the arrangement of nuclei in rows or palisades, but the specificity of this structure for neurinomas has been questioned, since it is also found in other, usually mesodermal, tissues. The author examined ten neurinomas. He regards mechanical factors as the cause of the palisade arrangement of nuclei in tissues with fibrillar structure. In smooth muscle, contraction and hyalinization or other regressive changes are responsible, in neurinomas the abundant growth of fibrils pushes the nuclei into this position. The palisades found in these tumors can, however, be distinguished from others by the characteristic ground substance, consisting of delicate parallel fibrils. Two types of tumors have been described, which, the author finds, represent different lines of development rather than successive stages.

B R LOVETT

BRAIN CYSTS W SCHLEY, Virchows Arch f path Anat **265** 665, 1927

Schley described six cases of cysts of the brain, in all of which a tumor, usually a glioma or angioma, was found. He agrees with Lindau's view, that these cysts arise by transudation of fluid from a preexisting tumor, due to disturbances in circulation. The tumor tissue may be discoverable only with the microscope. Not only angiomas and gliomas, as described by Lindau, may lead to cyst formation, but other types as well, in one instance a metastatic growth from a bronchial carcinoma. The vascularity of the tumor and disturbances in

the local circulation are the determining factors. While cysts have usually been found in the cerebellum, they may arise in the cerebrum or pons in the same manner, as described in two of the author's cases

B R LOVETT

**PATHOLOGY OF THE CEREBRAL VESSELS. I. CEREBRAL HEMORRHAGE. E POLLAK and P REZEK, Virchows Arch f path Anat 265 683, 1927**

Four instances of extensive hemorrhages of the brain were investigated pathologically, with reference to the theory of Westphal and Baer. According to this, a spasm of the vessels leads to anemia and autolysis of the wall, followed by increased permeability and bleeding, an acute rather than a chronic process. The authors found marked differences in the condition of the vessels at varying distances from the hemorrhagic zone. In this zone itself, the walls were entirely necrotic, and no cellular reaction was visible. At the border, the beginning of cellular reaction could be seen, but edema with splitting of the vessel wall was the chief change. Still farther away, partial necrosis was found, involving only a single coat, usually the media or elastic tissue, or only a short section of the vessel. Accumulations of cells surrounded the necrotic foci.

While it was not possible to draw conclusions as to the mechanism of cerebral hemorrhage from these morphologic changes, the authors found them incompatible with the theory of Westphal and Baer. The picture was that of a chronic process of long duration leading to a partial necrosis of the blood vessel walls. Sometimes marked necrosis of the media was found without any surrounding hemorrhage. Of the older theories, rupture of a vessel wall or the formation of small aneurysms as causes of bleeding could not be substantiated either. The authors regard vasomotor disturbances as an important factor, with the partial necrosis of the wall impeding its response to changes in a blood pressure already high. Consequent splitting of the layers permits the passage of blood through the wall.

B R LOVETT

**LYMPHATIC REACTION IN THE WALL OF THE APPENDIX. K NISHIKAWA, Virchows Arch f path Anat 265 735, 1927**

Nishikawa examined serial sections of 111 appendices for the presence of lymphatic tissue in the regions where this is not found normally, namely, in the muscularis, subserosa, serosa and the mesentery. In sixty-one cases he found lymphatic tissue in successive stages of development, from simple collections of lymphocytes to fully mature nodes, with capsule, germinal centers and sinuses. This reaction was shown to be independent of age and of variations in the lymphoid tissue of the mucosa. It was associated with chronic and with recurring inflammations, and was present in the stage of healing, but never during acute inflammations. It appeared to be not a part of the inflammatory process itself, but a secondary process, continuing independently of the inflammation.

B R LOVETT

**RENAL CHANGES IN NUTRITIONAL DISTURBANCES OF INFANTS. H STROHE, Virchows Arch f path Anat 265 765, 1927**

Histologic examination of the kidneys of fifty-six infants dying with nutritional disturbances revealed in the cortex thickening of the capsular epithelium, exudation into the capsular space, cloudy swelling, fatty changes and cellular infiltrations, especially around the blood vessels. The changes in the medulla were more extensive. All the changes of circulatory disturbance were observed, from hyperemia, with and without degenerative changes in the surrounding parenchyma, stasis with necrosis of the tubular epithelium, serous or cellular exudation into the interstitial tissue to degenerative changes (hyalinization, etc.), and cellular proliferation. Exudation of red cells into the interstitial tissue was frequent, and

consequent pigmentation in older cases Hemorrhagic infarction, and less frequently purulent interstitial nephritis, form the end-stage which may follow the foregoing changes Different stages were found at times in the same kidney, and often the two kidneys presented different appearances The presence of bacteria in the blood bore no relation to the renal changes In most fatal diseases of infants such changes are to be found, and are probably related to the disturbance in nutrition When extensive and productive of clinical symptoms, the condition may be referred to as nephritis of infancy

B R LOVETT

ANGIOSPASM AS A CAUSE OF RENAL INFARCTS K NEUBURGER, *Virchows Arch f path Anat* **265** 789, 1927

The author made a study of functional disturbances of the circulation as a cause of infarcts in the kidney Several ischemic infarcts were examined, in which no thrombosis and no disease of or injury to the vessel walls was present, and the conclusion reached that spasm of the renal artery, following operative trauma in the vicinity, was the most probable cause An instance of gangrene of the leg following an injection of hexatone in an infant with whooping cough was also attributed to traumatic angiospasm

B R LOVETT

MORPHOLOGY AND MICROCHEMISTRY OF THE ANIMAL CELL DEMONSTRATION OF THE CELL MEMBRANE M GUTSTEIN, *Virchows Arch f path Anat* **265** 805, 1927

Several staining methods are described for demonstrating the membrane system of the cell, including the membrane of the cell itself, of the nucleus, and of the nucleolus Either an acid (tannin) or a basic (alum) mordant is used, followed by a stain of the opposite reaction Since the three membranes, as well as certain protoplasmic granules, are all stained by these methods, there must be some similarity in their chemical structure That the granules are not artefacts could be shown by their presence also in supravitaly stained preparations Both acid and basic substances are present in the cell membranes Experiments in solubility in different fluids give the following results The acid body is a lipid, bound to the basic ground substance The acid mordant combines with the latter, the basic mordant with the acid lipid This lipid resembles the phosphatids in its staining reactions The same methods can be used for staining bacteria

B R LOVETT

RELATIONS BETWEEN OXYDASES, VITAL STAINING, POSTMORTEM STAINING, AND MORPHOLOGY OF THE CELL W LOELE, *Virchows Arch f path Anat* **265** 827, 1927

Loele finds that oxydases and peroxydases, which can be demonstrated by different phenolase reactions, are not uniform bodies, but mixtures of substances They may occur independently of each other Oxydases are not necessary for vital staining, but oxydase-containing substances lend themselves easily to staining by vital methods The process need not cause cell injury, especially if an acid stain is used By means of the secondary naphthol reaction, different types of cell nucleoli can be distinguished a single round body, several round ones, irregular and variable bodies and nuclei without nucleoli The alterations of the nucleoli of a single cell type during a disease process are described, and further morphologic changes in nucleoli and chromosomes

B R LOVETT

ALEUKEMIC MYELOSIS WITH OSTEOSCLEROSIS OF THE SKELETON A JORES, *Virchows Arch f path Anat* **265** 845, 1927

Jores described a case of hematopoietic disease, corresponding to aleukemic myeloid leukemia, of twelve years' duration, accompanied by sclerosis of the entire

bony system. In the much narrowed marrow cavities, there was both fibrous and actively functioning marrow. He regarded the disease of the marrow as primary, with the bony changes secondary to it.

B. R. LOVETT

**PATHOLOGIC PHYSIOLOGY OF GOITER.** B. BREITNER, Transactions of the International Conference on Goiter, Bern, Switzerland, Aug. 24-26, 1927. Edited by Hans Huber, Bern, 1928.

A comparison of the iodine content of the blood of the arteries and veins of the thyroid gland and the veins of the arm with that of the goiter appears to prove the existence of a thyroidal secretion escaping into the blood current. Results of experiments made by infusing specimens of blood from these different sources into the larvae of salamanders, point in the same direction. The action of iodine on persons with goiter corresponds to that which has been observed by experiments on animals. Subjects who are to be treated with iodine should therefore be carefully selected.

Clinical and experimental observations agree as to the morphologico-functional types of goiter conditioned by "hyporrhoe" and "hyperhorrhoe." The author's point of view is based (1) on the appreciation of the two principal functions of the thyroid gland, namely, the production and the elimination of secretion and on the functional adaptation of the gland and (2) on the discrimination between the activity and the output of this organ. Bearing in mind the rôle of the sympathetic nervous system in the secretory process of the thyroid gland, this point of view enables him to establish a complete theoretic schema of the functional diseases of the thyroid gland.

**ETIOLOGY AND EPIDEMIOLOGY OF THE ENDEMIC GOITER IN FRANCE.** L. BLARD and C. DUJET, Transactions of the International Conference on Goiter, Bern, Switzerland, Aug. 24-26, 1927. Edited by Hans Huber, Bern, 1928.

In France, thirty-seven departments are subject in varying degrees to endemic goiter, in the other forty-nine departments goiter is only exceptionally encountered. The geographical distribution of goiter in France has not changed during the past thirty years.

Altitude and climate play only a subsidiary part in the genesis of goiter. This is proved by the fact that goiter has decreased in intensity though its geographical distribution has remained the same. No systematic preventive treatment with iodine has come to light. The cause of the decrease is assumed to be (a) the improvement of the drinking water, (b) the increase in the consumption of wine, (c) emigration (temporary or permanent) from the goitrous districts, (d) a decrease in the number of marriages between blood relations, and (e) the improvement in the general conditions of living (personal and general hygiene and improvement of conditions in the home and of nourishment).

Although there are several causes of endemic goiter, drinking water is the most prominent. There are beyond all doubt certain kinds of water which produce goiter. The action of goiter-producing water is to be explained by its interference with iodine metabolism, causing relative or complete insufficiency of iodine. All factors therefore which increase the need of the system for iodine favor the appearance of goiter (puberty, pregnancy, lactation and the climatic period). Goiter is regarded not as a disease strictly confined to the thyroid gland, but as a general disturbance of nutrition.

The type of endemic goiter that is usually found in France is struma nodosa parenchymatosa or cystica. Diffuse hyperplasia of the thyroid gland is only rarely observed. Toxic goiter is rare. New growths of the thyroid gland are also rare. In carcinoma of the thyroid gland, 85 to 90 per cent of the cases occur as a result of an already existing goiter.

AUTHORS' SUMMARY

## Microbiology and Parasitology

EPIDEMIOLOGIC AND BACTERIOLOGIC INVESTIGATION OF THE SLOANE MATERNITY HOSPITAL EPIDEMIC OF HEMOLYTIC STREPTOCOCCUS PUERPERAL FEVER IN 1927 F L MELENEY, ZUNG DAU ZAU, H ZAYTOZEFF and H D HARVEY, Am J Obst & Gynec **16** 180, 1928

During the period from Jan 18 to Feb 18, 1927, an epidemic of puerperal fever raged in the Sloane Maternity Hospital, approximately 15 per cent of all pregnant patients developed the disease, with an approximate mortality rate of 33 per cent. The lochial discharges of all except one of the mothers affected revealed *Streptococcus hemolyticus*. Five of the strains were proved antigenically identical by cross agglutination and by crossed absorption of the agglutinin tests. Nineteen other strains were closely related to if not identical with the aforementioned strains. Some of the nurses and doctors were found to be carriers of these organisms, harboring them in the nose or throat. On serologic study the strains from the nose of one of the nurses was found identical with the puerperal strains. From an axillary abscess of a nurse whose finger was pricked, and from the peritoneal exudate of another nurse with peritonitis, strains were obtained which were like the five identical strains from the patients with puerperal fever. Cultures of the air of the wards and operating rooms, cultures of linen supplies and sterilized supplies yielded no hemolytic streptococci. The peak of fever, indicating the clinical onset, occurred usually on the fourth day. The vagina was considered the portal of entry and the organisms were conveyed to the patient by carriers.

A J KOBAK

THE BACTERIAL CONTENT OF THE UTERUS AT CAESAREAN SECTION II J W HARRIS and J H BROWNE, Am J Obst & Gynec **16** 332, 1928

Twenty-two among fifty uteri from which cultures were obtained at cesarean section were found to be infected. After six hours of labor the authors found that the amniotic cavity was invariably infected, even though the fetal membranes were intact. The second part of this report describes the bacteria that were recovered. Streptococci in numerous strains, *Staphylococcus albus* and diphtheroids were found most frequently. All the patients but one had a febrile puerperium, but all recovered. Healing of the incision was retarded when it contained any of the bacteria recovered in the amniotic contents.

A J KOBAK

SEPTICEMIA DUE TO A STRAIN OF THE BACILLUS MUCOSUS IN DIABETES MELLITUS E H MASON and W M BEATTIE, Arch Int Med **42** 331, 1928

Septicemia from *Bacillus mucosus* has been reported in seventy-eight cases. In the case reported here blood culture gave a capsulated organism considered a variant of the *B. mucosus* group. The infection occurred in a case of food-controlled diabetes and resulted in death in about two weeks.

HAMILTON R FISHBACK

BRONCHOMONILIASIS W R GALBREATH and C WEISS, Arch Int Med **42** 500, 1928

Monilia infection of the lungs may be of a mild, intermediary or severe form. The symptoms in general are dyspnea, cough, expectoration, with or without blood, and fever. There are frequent remissions and exacerbations. In the severe type the course resembles that of pulmonary tuberculosis and almost invariably ends fatally. Potassium iodide is the specific remedy. Other treatment may be the same as for tuberculosis. Monilia may be recovered from the sputum, or from the lesions at autopsy. A case is reported with a history of pulmonary

symptoms since 1918, the patient now being in a good state of nutrition and continuing his occupation. *Monilia psilosis* (ashfordi) has been repeatedly found in the sputum

HAMILTON R FISHBACK

SYNOVIAL FLUID IN CHRONIC ARTHRITIS C E FORKNER, A R SHANDS and M A POSTON, Arch Int Med 42 675, 1928

In a study of sixty-three cases of chronic arthritis, excluding syphilitic and tuberculous infections, positive cultures were obtained in 22 per cent. Cultures from the lymph nodes were positive in 48 per cent of twenty-one cases, in 24 per cent the same type of organism was recovered from joint and lymph nodes. In all cases, the number of white cells was increased, the bacteriologically positive cases showing almost twice as many as the negative cases. The number of polymorphonuclears was increased in the positive group, while the monocytes and lymphocytes predominated in the negative group. Synovial mesothelial cells were not seen constantly.

HAMILTON R FISHBACK

SYPHILIS OF THE STOMACH H A SINGER and F G DYAS, Arch Int Med 42 718, 1928

A case is detailed with a primary clinical diagnosis of gastric syphilis. Following roentgen examination and associated observations of ulcer, a partial gastrectomy was performed. Multiple ulcers were found. No classic gumma was present, and *Spirochaeta pallida* could not be demonstrated. Below the ulcers, in which fusospirilla of Vincent were present, the principal lesions were in the thickened submucosa. There were focal granulomatous lesions which were composed chiefly of lymphoid and plasma cells, with a marked perivascular distribution. No case has been found in the literature which meets the demands for a pathologic diagnosis of gastric syphilis, that is, the presence of a classic gumma, or the certain demonstration of *Spirochaeta pallida*.

HAMILTON R FISHBACK

A STUDY OF MICROCOCCUS ZYMOGENES MARTIN FROBISHER, JR, and E RANKIN DENNY, J Bact 16 301, 1928

The resemblance of the organisms studied as *Micrococcus zymogenes* to *Streptococcus liquefaciens* is such as to suggest that the former are merely varieties of the latter or that the two are identical. *M. zymogenes* should be classed as a streptococcus. The proteolytic enzymes of these organisms resemble histase in their action on cooked meat but differ from this enzyme in their ability to digest coagulated serum, gelatin and casein as well. There appears to be no relation between hemolysin and proteolytic enzyme production by these organisms. The literature reveals nothing to suggest a direct relationship between *M. zymogenes* and any special type of pathologic condition, although organisms called *M. zymogenes* have been more frequently isolated from endocarditis than from any other single disease. Proteolytic streptococci of the type represented by *S. liquefaciens* might be more frequently reported in pathologic bacteriology if more detailed study of the proteolytic activity of streptococcus-like organisms were made as a routine.

AUTHORS' SUMMARY

SUSCEPTIBILITY OF ESKIMOS TO THE COMMON COLD AND A STUDY OF THEIR NATURAL IMMUNITY TO DIPHTHERIA, SCARLET FEVER AND BACTERIAL FILTRATES PETER HEINBECKER and EDITH I M IRVINE-JONES, J Immunol 15 395, 1928

Eskimos are very susceptible to infections of the upper respiratory tract on contact with the outside world. Ordinary bacterial infections rarely occur. Diphtheria and scarlet fever are unknown clinically. In a group of about fifty subjects all gave negative reactions to the Dick test and also, in the case of the adults, to the Schick test. Children up to the age of 12 years invariably gave positive reactions to the Schick test. Three serums were found to contain antitoxin both

for diphtheria and for scarlet fever. It is therefore concluded that the immunity to the disease and the negative reaction to the skin tests depend on the presence of antitoxin. This is interpreted as being due to a natural hereditary immunity dependent on some nonspecific antitoxic mechanism. Skin reactions with filtrates of streptococci isolated from cases of rheumatic fever were mildly positive in a small percentage of cases. Neutralizing antitoxin was demonstrated in all three serums but it was not invariably present for all three toxins. The Eskimos showed a high percentage of positive reactions when tested with a *Staphylococcus aureus* filtrate.

AUTHORS' SUMMARY

INFECTION OF A LABORATORY WORKER WITH *BACILLUS INFLUENZAE* JOHN E WALKER, J Infect Dis 43 300, 1928

The course of a laboratory infection with Pfeiffer's bacillus is described. The symptoms consisted of rhinitis, conjunctivitis and bronchitis. There was no fever. Organisms serologically identical with the laboratory strain were isolated from the nose, conjunctivae and sputum. The disease would ordinarily be classified as a severe cold, though the diagnosis of sporadic influenza cannot be entirely eliminated. The infection demonstrates anew that some strains of the organism have an extraordinary avidity for attacking the mucous membrane of the respiratory system as the primary cause of disease.

AUTHOR'S SUMMARY

*STAPHYLOCOCCUS AUREUS* CONJUNCTIVITIS OF THE NEW-BORN ARTHUR B THOMAS, J Infect Dis 43 306, 1928

An acute purulent conjunctivitis may occur in infants without evidence of a preexisting vaginitis in the mother. In 100 consecutive cases of purulent conjunctivitis of new-born infants, none appeared to be caused by the gonococcus. Cultures of *Staphylococcus aureus*, isolated from the conjunctivitis and some other lesions that were present, seemed to belong to a single strain and were atypical in staining qualities, metabolic reactions with carbohydrates, and in pathogenicity for animals. This organism was considered to be the causative agent in all the cases and was probably transmitted through contaminated olive oil or boric acid or both.

AUTHOR'S SUMMARY

CHEMICAL AND BACTERIAL INHIBITION OF GAS FORMATION IN BACTERIAL CULTURES MITSUTERU ISHIKAWA, J Infect Dis 43 311, 1928

Subcarbonate, subgallate, nitrate, subnitrate of bismuth, ammonium and sodium benzoates, potassium bichromate, potassium chlorate, sodium fluoride, sodium iodate, ammonium and sodium nitrates and sodium salicylate definitely suppress the evolution of gas, not only from carbohydrates by single cultures of gas-producing bacilli and by three types of associate cultures (a gas-forming with an acid-producing organism, an aerogenous bacillus with a proteolytic organism, and gas-forming and acid-producing organisms with a proteolytic bacterium), but also from sodium formate by pure cultures of aerogenous bacteria. The inhibitory effect of the paratyphoid bacillus on gas production of the colon bacillus appears to depend, partly at least, on a deficiency of proper nitrogenous substances apparently resulting from the metabolic activity of the paratyphoid bacillus.

AUTHOR'S SUMMARY

INFLUENCE OF IODIDE ON BACTERIAL DECOMPOSITION OF NITROGENOUS SUBSTANCES MITSUTERU ISHIKAWA, J Infect Dis 43 321, 1928

Potassium iodide and potassium iodate exert an inhibitory effect on the formation of ammonia by proteolytic organisms of a gelatin culture and on the production of amino-acids by the proteolytic bacteria-free enzyme. In this effect, potassium iodide has practically no demonstrable selective action. Different bacteria are affected almost equally by the presence of the iodide. The liberation of

ammonia from urea by ureasplitting bacteria, cultured or washed, is decreased under the influence of the iodide, apparently, through an inhibitory effect on the activity of the enzymes

AUTHOR'S SUMMARY

THE THERMAL DEATH POINT OF *BRUCELLA ABORTUS* IN MILK RUTH BOAK  
and C M CARPENTER, J Infect Dis 43 327, 1928

The thermal death point of eight strains of *Brucella abortus* of porcine, human and bovine origin grown in milk was variable. The porcine strain was most resistant. An exposure of fifteen minutes at 140 F (60 C) destroyed the human and bovine cultures that were examined. The porcine strain, however, was still viable at this temperature.

The injection of guinea-pigs was more reliable than cultures for determining the viability of *Brucella abortus* in milk.

AUTHORS' SUMMARY

CLASSIFICATION OF *BACTERIUM ALCALIIGENES*, *PYOCYANEUM* AND *FLUORESCENS*  
BRUNO LEO MONIAS, J Infect Dis 43 330, 1928

A microbiologic collection of thirty cultures has been classified systematically on the basis of morphology and of biochemical reactions with special reference to their relationship to two main groups of bacteria, the one group related to *Bacterium coli*, and the other to *Pseudomonas mrigula*.

AUTHOR'S SUMMARY

COMPARISON OF GLYCEROL AND BRILLIANT GREEN BILE FOR TREATMENT OF  
FECES FOR ISOLATION OF TYPHOID ORGANISMS LEON C HAVENS and  
CATHERINE RIDGWAY, J Infect Dis 43 345, 1928

Six hundred and sixty-one specimens of feces containing known numbers of typhoid bacilli were inoculated into both 30 per cent glycerol and brilliant green bile. Positive results were obtained in 43 per cent of the specimens in glycerol, and in 75 per cent in brilliant green bile. Dosages of at least 100,000 typhoid bacilli per one-tenth gram of feces are necessary to obtain consistently positive results in glycerol, while one tenth of this number will yield the same percentage of recoveries from brilliant green bile. In glycerol the minimal detectable number of typhoid bacilli in feces appears to be 10,000, in brilliant green bile, 1,000. The effect of the age of the specimen has been studied. Specimens in brilliant green bile show a slight decrease in positive results for forty-eight hours, while the typhoid bacilli in the same specimens in glycerol disappear rapidly.

AUTHORS' SUMMARY

SEPTIC INFECTION DUE TO *BACTERIUM MORGANI* L T THJOTTA, J Infect  
Dis 43 349, 1928

A case of septic infection due to *Bacterium morganii* is reported which originated in the gallbladder and terminated fatally on the twelfth day after the onset of acute symptoms. *B. morganii* was isolated from the gallbladder and from the blood. The patient's serum agglutinated the organism in a dilution of 1:320. *B. morganii* is generally considered a nonpathogenic, rare type of *Bacillus coli*, which under certain conditions, may become highly virulent. The generic name, *Salmonella morganii*, is found to be inappropriate. This organism should properly be called either *B. morganii*, *B. metacoli* or *Escherichia morganii*.

AUTHOR'S SUMMARY

BACTERIOLOGIC AND BACTERIOPHAGIC STUDY OF INFECTED URINES JANET  
ANDERSON CALDWELL, J Infect Dis 43 353, 1928

In the classification of 112 cultures of bacilli from infections of the urinary tract, a group of 12 aerobic, gram-negative bacilli which produce spores was



recognized and described Seventeen cultures related to fluorescent bacilli were also described

Sewage filtrate produced marked lysis of 74 per cent of the 100 nonspore-forming cultures and failed to produce lysis of 7 per cent These 100 cultures were classified into colony types on the basis of dissociative changes The susceptibility of the various dissociative types to lysis by sewage filtrate was tested The results strongly indicated that there is no stage of dissociation of urinary bacilli which is resistant to bacteriophagic action

Native bacteriophage could be demonstrated in the filtrates of twenty-six of the 100 urines in 20, only two passages were required It can be demonstrated about as often with the organism found in the same urine as by using stock cultures of colon and dysentery bacilli Native bacteriophage was found associated with every cultural group, with cultures in every stage of dissociation, and with cultures having all degrees of sensitiveness to lysis Therefore, contact with bacteriophage in the body does not produce in a culture resistance to lysis or any constant change in its growth characteristics, nor does it force the culture into any one stage of the dissociation cycle

AUTHOR'S SUMMARY

PRODUCTION OF HISTAMINE, TYRAMINE, BRONCHOSPASTIC AND ARTERIOSPASTIC SUBSTANCES IN BLOOD BROTH BY PURE CULTURES OF MICROORGANISMS  
KARL K KOESSLER, MILTON T HANKE and MARY S SHEPPARD, J Infect Dis 43 363, 1928

This paper contains a report on the production of histamine, tyramine, bronchospastic and arteriospastic substances by 223 micro-organisms grown on a blood-broth medium Ninety-four are members of the colon-typhoid group Nine of the organisms convert histidine into histamine, of these, two belong to the *Escherichia* group, and seven to the *Salmonella* group Five of the eight *Salmonella morganii* strains produce histamine Tyramine was not produced in this group The faculty for producing bronchospastic and arteriospastic substances other than histamine is highly developed in the colon-typhoid group of micro-organisms Of 49 *Salmonella* studied, 38 produced spastic substances, of 6 dysentery *Shiga* studied, 5 were spastic, of 12 paradysentery studied, 6 were spastic, of 9 *Escherichia* studied, 9 were spastic, and all of the typhoid bacilli studied were spastic Taken collectively, of the 94 representatives of the colon-typhoid group studied, 67 produced spastic substances

Bronchospastic and arteriospastic substances are rarely produced by micro-organisms other than those belonging to the colon-typhoid group Histamine was not produced by any of the 129 micro-organisms that are not members of the colon-typhoid group Of these 129 micro-organisms, 5, all of them streptococci, produced tyramine

AUTHORS' SUMMARY

THE METABOLISM OF LEISHMANIA TROPICA A J SALLE and CARL L A SCHMIDT, J Infect Dis 43 378, 1928

A solid and a liquid medium were prepared for the cultivation of *Leishmania tropica* The growth on the liquid medium was sufficient for the determination of the metabolic activities of *Leishmania tropica* The organism was grown on the standard medium and on mediums in which certain described variations were made The analytic data indicated that the metabolism of *Leishmania tropica* does not differ essentially from that of many bacteria Carbohydrate exerts a marked sparing action toward the protein of the medium The organism possesses marked proteolytic powers Its utilization of protein was demonstrated by an increase in the ammonia content of the medium and a rise in  $p_H$  Its utilization of protein was demonstrated also in an increase of split-protein products Experiments showed that this organism cannot survive under anaerobic conditions The function of hemoglobin in the medium may be to contribute an accessory factor of food or growth

AUTHORS' SUMMARY

INTRANASAL INOCULATIONS OF RABBITS WITH *BACILLUS INFLUENZA* JOHN E WALKER, J Infect Dis **43** 385, 1928

Following the intranasal inoculation of rabbits with a recently isolated strain of Pfeiffer's bacillus, it was possible to recover the organism from the nasal cavities of the animals for periods of from four to fifteen days. Two animals so inoculated showed a nasal discharge at the time when the organisms were most numerous. The inoculation was followed by the appearance of agglutinins in the blood stream. Animals once infected were immune to reinfection. After two months' cultivation, the strain lost its ability to attack the nasal mucous membrane of rabbits. Two other strains of Pfeiffer's bacillus were tested and were found unable to produce infection. Failure to produce disease with Pfeiffer's bacillus is demonstrated experimentally to be due either to immunity of the host as a result of previous infection or to lack of virulence on the part of the organism.

The fluctuations in the virulence of the organism and in the resistance of the host fit in well with what would be expected of the etiologic agent of epidemic influenza. These facts, together with the now well substantiated ability of the organism to produce primary respiratory disease of the cold-influenza type, are believed to relate Pfeiffer's bacillus to the etiology of epidemic influenza more closely than ever.

AUTHOR'S SUMMARY

MICROORGANISMS OF LUNG ABSCESS AND BRONCHIECTASIS LUCILLE H ERMATINGER, J Infect Dis **43** 391, 1928

The bacteriologic examinations in thirty-three cases of chronic and acute abscess of the lung and bronchiectasis disclosed the pyogenic organism, *Staphylococcus aureus* in 75.4 per cent of the total number of cases, hemolytic streptococci in 55.3 per cent and pneumococci in 19.4 per cent. A spirochete, apparently falling into the *Leptospira* group, according to Noguchi's classification, was obtained from the case reported and was kept alive in a mixed culture containing bacteria, for a period of fourteen days.

AUTHOR'S SUMMARY

ABSENCE OF INFECTIVITY IN FILTERED URINE FROM DIABETIC PATIENTS G HAROLD ETINGER and GUILFORD B REED, J Infect Dis **43** 399, 1928

Fresh urine from diabetic patients, filtered (Berkefeld) and injected into fourteen rabbits and seven dogs, caused no appreciable change in the percentage of blood sugar for periods of from 55 to 236 days. Aerobic and anaerobic cultures had similar negative results during periods up to 63 days. Small amounts of reducing substances were found occasionally in the urine of some of the rabbits, but not in excess of amounts found in the control animals. There was never any suggestion of interference with carbohydrate metabolism.

The urine was obtained from eight patients with diabetes, ranging in age from 12 to 55 years and with histories of diabetes for from three weeks to fifteen months. It may be presumed that if the urine of a diabetic patient contains a causal organism it would be present during this period. The conclusion is that the filtered urine of a patient with diabetes contains no organism which can reproduce the diabetic condition in dogs or rabbits.

AUTHORS' SUMMARY

GROWTH OF PARAMECIA IN PURE CULTURES OF PATHOGENIC BACTERIA AND IN THE PRESENCE OF SOLUBLE PRODUCTS OF SUCH BACTERIA CHARLES HUGHES PHILPOTT, J Morphol **46** 85, 1928

Virulent hay-infusion cultures of *Bacillus pyocyaneus* are toxic to pure-line races of three species of paramecia, but these races may acquire a tolerance for this toxic agent. Races with acquired tolerance have been grown for long periods of time in toxic, pure cultures of *B. pyocyaneus* by means of the daily-isolation culture, and here the average division rate is as high as, or higher than, in the chance-mixed bacterial cultures in which these protozoa are usually maintained in

the laboratory The tolerance is lost, however, when the paramecia are removed from the toxic cultures and grown for a number of generations in cultures of nontoxic bacteria

The toxic agent that is lethal to paramecia is probably the soluble toxin of *B. pyocyaneus* The investigation shows that the agent is soluble and either thermolabile or volatile It also shows that all deleterious substances, other than the soluble toxin, known to be produced in cultures of this bacillus, are nonlethal to paramecia

Hay-infusion cultures of *Bacillus enteritidis* were lethal to paramecia All attempts to develop tolerance in paramecia for the toxic agent in these cultures failed

Under the experimental conditions that prevailed, diphtheria toxin was found to have no appreciable effect on the division rate or death rate in three species of paramecia

#### AUTHOR'S SUMMARY

#### OBSERVATIONS ON THE GRAM-NEGATIVE COCCI OF THE NASOPHARYNX, WITH A DESCRIPTION OF NEISSERIA PHARYNGIS G S WILSON and MURIEL M SMITH, J Path & Bact **31** 597, 1928

Seventy-eight strains of gram-negative cocci, other than meningococci, have been studied on a series of mediums, and their colonial appearance, growth in serum broth and fermentation reactions noted On ascitic agar plates after forty-eight hours' incubation the colonies may be divided into smooth and rough types, but after five days many of the primarily smooth colonies undergo a transformation into the rough type Experiments have shown that one and the same strain may be dissociated into smooth and rough variants, and that smooth variants may be recovered from a pure culture of a rough variant The growth in serum broth after twenty-four hours is subject to great variation in appearance, but, on the whole, the permanently smooth colonial types give rise to a powdery or finely granular deposit, and the primarily and secondarily rough types to a coarsely granular deposit often accompanied by a surface ring growth The fermentation reactions have been tested in litmus ascitic agar sugars and in serum peptone water sugars containing Andrade's indicator In only one half of the fifty strains examined in both mediums were the results in agreement It is concluded that the cultural and biochemical characters of the gram-negative cocci are subject to such variation that they cannot justifiably be used for purposes of classification in the way in which they have hitherto been employed It is suggested that instead of dividing them into a number of so-called species catarrhalis, flavus, cinereus, mucosus and siccus, they should be grouped under the broad term *Neisseria pharyngis*, the characteristics of which are enumerated It seems possible, in the light of S P Wilson's work that within this group there may be subgroups the characteristics of which, though subject to a certain amount of variation, are yet sufficiently constant to allow of their differentiation Further work, however, is necessary before the delimitation of these subgroups can be laid down

#### AUTHORS' SUMMARY

#### THE PATHOGENIC VALUES OF PNEUMOCOCCAL TYPES THE LESIONS PRODUCED IN RELATION TO VIRULENCE J F GASKILL, J Path & Bact **31** 613, 1928

The sequence of lesions produced in the lung with rise of titer is similar with all pneumococci The pathogenicity of type II strains, however, is lower than that of type I in both mice and rabbits Not only is it harder to reach a given titer in mice, but the lesions produced at that titer are of lower grade than those produced by type I The pathogenicity of type III strains is lower for mice, rabbits and man, it is again harder to reach a given titer for mice, and less severe lesions are produced in the lung of the rabbit at that titer than with type I The pathogenicity of group IV organisms, which are virulent and have been obtained from severe lesions, is, if anything, higher than that of type I Such organisms are therefore quite as dangerous as type I and as easily raised to a virulent titer

#### AUTHOR'S SUMMARY

HISTAMINE AND INFECTION. G MARSHALL FINDLAY, J Path & Bact **31** 633, 1928

It is suggested that the well known relationship between injury and the localization of organisms in injured tissue is due to the liberation by injured tissue of histamine or a histamine-like substance which causes dilatation of the capillaries and increased permeability of the capillary endothelium with the result that organisms present in the blood stream are enabled to escape into the surrounding tissues. Evidence in support of this theory is brought forward in experiments with the viruses of fowl pox, vaccinia and the Rous sarcoma, *Staphylococcus aureus*, streptococcus and pneumococcus

AUTHOR'S SUMMARY

A CASE OF ENDOCARDITIS IN MAN, ASSOCIATED WITH *BACILLUS PARAINFLUENZAL*, RIVERS, 1922 DOROTHY S RUSSELL AND PAUL FILDES, J Path & Bact **31** 651, 1928

A case has been described in which a subacute infective endocarditis was excited by a bacillus identified as *Bacillus parainfluenzae*, Rivers, 1922. The pathogenicity of the organism has been further established by the demonstration of multiple foci in the myocardium, brain and meninges in which emboli containing collections of these bacilli had lodged in arterioles and capillaries, causing a focal inflammatory reaction and hemorrhage. It is believed that this is the first instance of a causal relationship being demonstrated between this organism and disease in man.

AUTHORS' SUMMARY

THE TYPES OF TUBERCLE BACILLI IN HUMAN BONE AND JOINT TUBERCULOSIS  
A STANLEY GRIFFITH, J Path & Bact **31** 875, 1928

Tubercle bacilli have been isolated from 598 cases of tuberculosis of the bones and joints and their type determined. Bovine bacilli were found in 20 per cent of persons of all ages, in 33 per cent of children less than 5 years of age and in 24 per cent of children between the ages of 5 and 10 years. No patient more than 23 years of age yielded bovine bacilli. Bovine bacilli appear to account for a larger proportion of the cases of tuberculosis of the spine than other commonly affected bones and joints. Tuberculosis of bones and joints may be the result of either respiratory or alimentary infection.

AUTHOR'S SUMMARY

BACILLUS PROTEUS INFECTIONS JOHN F TAYLOR, J Path & Bact **31** 897, 1928

The name *Bacillus proteus* should be restricted to a well defined group of organisms. They are nonsporing, gram-negative, pleomorphic bacilli which produce a spreading or creeping growth on solid mediums. They are proteolytic and hemolytic. They do not ferment lactose, mannite or dulcitol, but ferment dextrose and saccharose and occasionally maltose. True indol may or may not be formed from peptone water. In milk, a transient clot is formed which is rapidly peptonized. In this investigation fifty-three strains recovered from human sources were examined by morphologic, cultural, biochemical and serologic methods. All these strains have the aforementioned characteristics. Only three of the strains fermented maltose, these same three strains alone produced true indol. Agglutination tests show variations between strains, absorption tests seem to show definite differences. *B. proteus* may produce severe infection in the human subject or may exist as a harmless saprophyte in the tissues, body fluids or excreta. An attempt has been made to classify the strains as pathogenic or nonpathogenic on the basis of the history, clinical course and bacteriologic observations in each case. Twenty-two strains have been classed as pathogenic, twenty-four as nonpathogenic and seven as doubtful. No classification into pathogenic and nonpathogenic strains could be made by the laboratory methods employed, and no differences were found between strains recovered from urinary, fecal or other sources. *B. proteus* "X 19"

of Weil and Felix was found to be serologically distinct from the fifty-three strains of *B proteus* collected, but otherwise resembled them closely

## AUTHOR'S SUMMARY

RESEARCHES ON ANTHRAX INFECTION AND IMMUNITY D COMBIESCO, Arch Roumaines de path exper et de Microbiol 1 81, 1928

Besredka and others have reported that anthrax infection in animals takes place only through the skin. In this work the possibility of other routes of infection is investigated in rabbits and guinea-pigs.

In the normal animal, the blood leukocytes engulf virulent anthrax bacilli and show negative chemotaxis for encapsulated organisms. In fresh serum, non-encapsulated bacteria undergo lysis, while encapsulated bacteria do not. In hyper-immunized animals, phagocytosis of encapsulated bacilli takes place. The negative chemotaxis for leukocytes that is exercised by encapsulated bacilli in the normal animal is due to the combined action of the capsule and the organism itself. Thus an attenuated bacillus, even though encapsulated, is phagocytosed, as is also a virulent nonencapsulated organism, but phagocytosis of bacilli which are both virulent and encapsulated does not take place.

The skin is not the only organ through which anthrax infection can take place. The experiments show that intravenous injection of bacilli in animals has no effect if the dose is small, less than 1 cm of emulsion, but with a larger dose, death occurs regularly. The bacteria are not all taken care of by the phagocytes, those that remain rapidly become encapsulated and acquire negative chemotaxis for leukocytes. This process is referred to as animalization. Injection with cultures developed in whole blood or inactivated serum similarly results in death, while those developed in fresh serum undergo lysis and do not cause infection. It is also found possible to infect by inoculating other organs directly, such as the lungs, liver and spleen. Intraperitoneal or subcutaneous inoculations also kill if the bacilli are protected from too rapid phagocytosis, and are given time to undergo animalization. This can be done by introducing them enclosed in capillary tubes open at one end, through an incision into the abdominal cavity or subcutaneous tissues. The tubes are broken at the end of several days, after animalization has occurred and the host dies. The histologic structure of the skin favors infection in a similar manner. A certain number of bacilli in the lacunar spaces of the dermis escape phagocytosis for some time, thus acquiring resistance to destruction. Results similar to these have been obtained by other experimenters.

GUINEA-PIG EXPERIMENTS WITH THE TUBERCULOUS FILTRATES M LINDEMANN AND BANG DSCHENG LI, Beitr z Klin d Tuberk 70 380, 1928

Forty-one guinea-pigs were given injections of sterile filtrates from sputum and pure cultures. Five of them developed positive tuberculin reactions. Only in three animals was it possible to demonstrate one acid-fast rod. Whether the acid-fast rods demonstrated were tubercle bacilli or not could not be decided.

MAX PINNER

NONACIDFAST FORMS IN SAPONIN-GLYCEROL BROTH CULTURES OF THE TUBERCLE BACILLUS O KIRCHNER, Beitr z Klin d Tuberk 70 385, 1928

In saponin-containing glycerol broth cultures, nonacid-fast organisms were found. These organisms constituted a strictly specific antigen in complement fixation.

MAX PINNER

EXPERIMENTAL TUBERCULOSIS IN NORMAL RATS K HAGEDORN, Beitr z Klin d Tuberk 70 389, 1928

Rats may be infected by large doses of bovine bacilli. The lesions appear differently than in other animal species. One finds an enlargement of the spleen.

and numerous pulmonary foci. The histologic characteristic is the presence of large numbers of foam cells. The infected rats usually do not react to tuberculin, but in the majority of cases their serum gives a positive complement-fixation test.

MAX PINNER

THE FILTRABILITY OF THE TUBERCULOUS VIRUS F. RABINOWITSCH-KEMPNER, *Ztschr f Tuberk* 52 18, 1928

One hundred and forty-six guinea-pigs received injections of filtrates from various tuberculous materials including pure cultures, sputum and exudates. Six of these animals developed generalized tuberculosis. In all six cases, the material was filtered through a membrane filter. All filtrates filtered through Chamberland filters did not produce tuberculosis. All cultures with filtrates remained sterile. In no case was it possible to demonstrate acid-fast rods in the glands or organs of healthy noninoculated animals. It must be assumed that the acid-fast rod is not the only shape of the tubercle bacillus. Under certain circumstances the development of the classic shape does not occur, but a microscopically invisible type develops the culture of which has so far not been successful. The virulence of this type must be low. A further report will deal with the conditions under which the typical type or filtrable virus develops.

MAX PINNER.

### Immunology

THE COMPLEMENTING PROPERTIES OF BLOOD PLASMA ROSCOE R. HYDE, *Am J Hyg* 8 859, 1928

A potent complement has been found in the blood plasma of a hemophiliac subject. It has also been demonstrated in other blood plasma which has been prevented from clotting by the use of heparin. In both cases the titer of the complement in the plasma was the same as in the serum from the same blood after clotting had occurred. These and other observations, for which experiments are described, demonstrate that complement must occur normally in the circulating blood, that it is not changed by the clotting of the blood or by injury of phagocytes and that it is a natural and not "an artificial principle" as claimed by d'Herelle.

PEARL ZEEK

PRECIPITIN REACTIONS WITH VARIOUS TISSUES OF ASCARIS LUMBRICOIDES AND RELATED HELMINTHS GRAEME A. CANNING, *Am J Hyg* 9 207, 1929

The data presented here indicate that certain isolated tissues, due to their composition and embryonic origin, are preeminently fitted to use in performing immunologic tests to trace biologic relationships of animals, whereas others not only are unsuitable but would tend to confuse the results. Thus, more delicate specific differences may be discovered between various ascarids by the use of a substance, like the egg, whereas more distant relations may be revealed by the use of sperm. From these things it follows that it is far better to find the most suitable tissue than to use the whole worm when conflicting elements would obscure the results.

FROM AUTHOR'S SUMMARY

IMMUNIZATION WITH R. PNEUMOCOCCI W. S. TILLET, *J Exper Med* 48 791, 1928

A broad immunity against infection with virulent *S. pneumococci* (Types I, II, III) can be induced in rabbits by vaccination with the degraded R strains of pneumococcus. This form of active resistance is effective in the absence of demonstrable type-specific antibodies and may be passively transferred to normal rabbits by the blood of the immunized animal.

AUTHOR'S SUMMARY

THE MODE OF ACTION OF A VIRICIDAL SERUM S P BEDSON, Brit J Exper Path  
9 235, 1928

Experiments are cited which warrant the conclusion that virus and neutralizing antibody unite in vitro

PEARL ZEEK

DILUTION PHENOMENON OBSERVED IN THE TITRATION OF THE SERUM OF FOWLS  
IMMUNIZED AGAINST THE VIRUS OF FOWL PLAGUE CHARLIS TODD, Brit  
J Exper Path 9 244, 1928

1 A mixture of fowl plague virus with the corresponding immune serum, so prepared as to be just nonvirulent when injected intramuscularly into a fowl, is rendered virulent by simple dilution with saline

2 This dilution phenomenon takes place even after the undiluted mixture has been kept at 37 C for four hours, showing that the action of the immune serum is not that of destroying the virus in vitro, but that the virus and immune bodies can exist side by side in the mixture without destruction of the former

3 Similarly, a mixture of the virus with just enough immune serum to render the mixture harmless to fowls when injected intramuscularly is found on intravenous injection to give rise to acute fowl plague, although the fowl is apparently not more susceptible to intravenous than to intramuscular injection of the virus

4 This behavior of mixtures of the virus with its immune serum resembles the behavior of toxin-antitoxin mixtures observed in the case of tetanus, diphtheria and certain other toxins

5 The dilution phenomenon is of practical importance in the titration of immune serums against the corresponding viruses, as the degree of dilution of the infected mixture may, within certain limits, influence the result of the injection

AUTHOR'S SUMMARY

EXPERIMENTS ON THE PURIFICATION AND CONCENTRATION OF SCARLET FEVER  
TOXIN PERCIVAL HARTLEY, Brit J Exper Path 9 259, 1928

Crude scarlet fever toxin was purified and concentrated by Walpole's method, and the active principle, which gives the characteristic skin reaction, was obtained in a highly purified and concentrated form This may possibly be a step toward the standardization of scarlet fever antitoxin, using this concentrated product as test toxin and the rabbit as biologic indicator

PEARL ZEEK

CONCENTRATION AND PURIFICATION OF STREPTOCOCCAL TOXIN J V PULVERTAFT,  
Brit J Exper Path 9 276, 1928

Filtrates from cultures of the Dochez strain of *Streptococcus scarlatinae* were prepared which were fatal for rabbits in doses of from 2.5 to 10 cc A method is described by which the toxin may be so purified and concentrated as to be lethal in doses as small as 0.1 cc Complete protection is afforded to rabbits against large doses of the toxin by streptococcal antitoxic serum, but tetanus and diphtheria antitoxins and normal horse serum have no effect

PEARL ZEEK

EXPERIMENTAL RESEARCHES ON THE NECROTIC LESIONS PROVOKED BY THE  
INJECTION OF MASSIVE DOSES OF BCG M J ZEYLAND and MME E  
PIASFCKA-ZEYLAND, Ann de l'Inst Pasteur 42 652, 1928

Rabbits and guinea-pigs were injected with 15 or 20 mg of BCG or with killed virulent tubercle bacilli by various routes, intravenous, intra-arterial, intracardiac, intrapleural, intraperitoneal and intrarenal Rabbits injected intravenously gave noncaseous follicles Guinea-pigs injected intraperitoneally showed

tubercles, sometimes caseous Part of the rabbits given an intracardiac injection and all given injections in the pleura or in the kidney gave tubercles with necrosis Necrotic lesions are secured experimentally when conditions permit an agglomeration of bacilli in the tissues This necrosis is due to endotoxins comparable to those of some of the acid-fast saprophytes "Under the conditions of vaccination, B C G is inoffensive"

M S MARSHALL

RESEARCHES ON SERUM ANAPHYLAXIS E SUAREZ, Ann de l'Inst Pasteur **42** 877, 1928

Euglobulin, pseudoglobulin and serum albumin act as different antigens, each sensitizes specifically and is toxic for animals sensitized with whole serum and with corresponding antigen The specificity of the neighboring fractions (pseudoglobulin-euglobulin, pseudoglobulin-serum albumin) is such that animals sensitized with one fraction resist from ten to fifteen lethal doses of the other fraction The specificity of the less related fractions (euglobulin-serum albumin) is such that animals sensitized with one resist from fifteen to eighty lethal doses of the other These antigens sensitize after different periods of incubation The minimum (nine to twelve days) proper for serum anaphylaxis is reduced in euglobulin anaphylaxis to from three to six days, it is from twelve to fourteen days in serum-albumin anaphylaxis, and from eight to ten days in pseudoglobulin anaphylaxis

AUTHORS' RESUME

REINFECTION OF TUBERCULOUS GUINEA-PIGS AND GUINEA-PIGS IMMUNIZED WITH B C G M E RIST and MLLF J MISIEWICZ, Ann de l'Inst Pasteur **42** 945, 1928

Virulent tubercle bacilli were inoculated subcutaneously or into the inguinal glands of a group of guinea-pigs, the survivors being used for reinfection All of another group inoculated with B C G survived All reinoculations were intraperitoneal in varying amounts In general, the results indicate that animals surviving virulent tubercle bacilli on reinoculation die sooner than the control animals—possibly a matter of allergy—whereas animals injected with B C G survived the second inoculation (virulent tubercle bacilli) longer than those in the control group

M S MARSHALL

RESEARCHES ON SERUM ANAPHYLAXIS E SUAREZ and W SCHAEFFER, Ann de l'Inst Pasteur **42** 1447, 1928

One may obtain regularly anti-anaphylaxis without shock, in this case, anti-anaphylaxis is more intense than that following shock One may obtain repeated shock (pure euglobulin) without having anti-anaphylaxis Between shock and anti-anaphylaxis there exists no relation of cause and effect, it is a question of concomitant phenomena capable of being dissociated Researches carried on with anaphylaxis and anti-anaphylaxis of various proteins of serum enable us to state that each of these is constituted of two groups of functions, sensitizing and toxic on one hand and anti-anaphylactic on the other hand These functions are not equally represented in each of the serum proteins The euglobulin is especially sensitizing and toxic, the anti-anaphylactic properties are insignificant or nil In the pseudoglobulin both functions are represented as in the whole serum The serum albumin possesses more anti-anaphylactic properties than toxic and sensitizing properties The toxic and sensitizing properties are strictly specific for each antigen, the anti-anaphylactic properties are common to several fractions of serum A heterologous fraction produced a better anti-anaphylaxis than a homologous fraction, the former requiring a heavier dose in injection than the latter

AUTHORS' SUMMARY



THE RELATIONSHIP BETWEEN STRUCTURE AND FUNCTION OF LIPOID ANTIGENS  
H. SACHS and G. BOCK, *Arb. d. Staats-Inst. f. exper. Therap.* **21** 159, 1928

Slow, fractional dilution of lipoidal extracts proved essential for their antigenic function in complement fixation. The quickly diluted extracts not only failed to fix complement but actually inhibited—by reaction as a “half haptene” with positive serums—the complement fixation otherwise produced by these serums with properly diluted extract. This inhibition was attributed to the state of fine dispersion of the lipid in suspension. Alcoholic extracts of guinea-pig kidney tested with rabbit antisera for the kidney extracts plus swine serum, and cholesterolized beef heart extract tested with Wassermann-positive serums from human beings were among the combinations tried in these tests.

ETHEL B. PERRY

CHEMOSPECIFIC ANTIGENS. A. KLOPSTOCK and G. E. SULTZER, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55** 118 and 450, 1928

Diazotized serums may be used as antigens, in which case the resulting antisera lose their species specificity almost completely and acquire a specificity for similarly diazotized serums from various species. Complex antigens prepared by treating serum with diazotized atoxyl or metanilic acid likewise yield antisera which give specific precipitation and complement-fixation reactions with serums from various sources treated with the same chemical compound. In these cases, addition of the simple chemical compound prevents the reaction of antigen and antiserum in the complement-fixation reaction.

Simple mixtures of serum and diazotized atoxyl may be used for active immunization, in which case the resulting antisera are strongly specific for the atoxyl, although they may also exhibit species specificity or even both types of specificity. The loss in species specificity of the complex antigens prepared by Landsteiner's method is due to the drastic treatment of the serum with acid, alkali and alcohol rather than to the formation of a compound with a new specificity for the added chemical group.

ARTHUR G. COLE

THE EFFECT OF SERUM ON THE ISOLATED VESSEL. P. INTROZZI, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55** 167, 1928

Introzzi continued the experiments of Friedberger on the constricting effect of normal, homologous and heterologous serum (rabbit, guinea-pig, rat, frog, carp, beef) on the isolated blood vessel of the guinea-pig, rabbit and rat. The constricting substances were present in the insoluble fraction of the albumin obtained by electro-osmosis. The irradiation of normal serum with ultraviolet rays caused a decrease or complete disappearance of the constricting principle. The vasoconstricting effect was not influenced by the state of digestion or starvation of the animal when the serum was obtained. The serum of tuberculous patients produced irregularly constriction of the isolated vessel of tuberculous guinea-pigs. Similar experiments with the urine of tuberculous persons gave negative results.

W. C. HUEPER

ANAPHYLAXIS OF ISOLATED VESSELS. E. FRIEDBERGER and P. INTROZZI, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55** 226, 1928

Using isolated sensitized vessel it was found that the antigenic serum loses its stimulating effect after heating at 100°C for thirty minutes, but is not demonstrably changed by irradiation with ultraviolet rays. The addition of eosin to the serum before irradiation does not change this result. Isolated vessels of guinea-pigs treated with sheep serum react more markedly on injection of the soluble fraction of albumin and euglobulin than of pseudoglobulin and the insoluble fraction of albumin. Passive immunity can be demonstrated on the isolated vessel of guinea-pigs and rats.

W. C. HUEPER

SKIN SENSITIZATION AS A MEANS OF STUDYING THE RELATIONS OF DIFFERENT SPECIES H FROLICH, *Ztschr f Immunitätsforsch u exper Therap* **55** 236, 1928

After a review of the methods for demonstrating biologic relations among different species of animals, the author reports his results from the intracutaneous sensitization of human skin as a method of differentiation. He tested the serum of (1) *Macacus rhesus* and *Macacus cynomolgus*, (2) beef, goat and sheep, (3) rabbit and guinea-pig, (4) white rat and white mouse, (5) chicken, pigeon, goose and turkey, (6) horse, mule and donkey and (7) pike, tench and bream. Biologic relations were established by this method among the animals in the different groups with the exception of those in groups 3 and 7. He succeeded in sensitizing the human skin against the serum of the lower monkeys. His results substantiated the results with other methods.

W C HUEPER

THE PRODUCTION OF PRECIPITATING ANTISERUM OF HIGH VALENCE GAELTGENS, *Ztschr f Immunitätsforsch u exper Therap* **55** 258, 1928

The author attempted to further the production of highly effective precipitating serum by the injection of India ink, but the results were favorable only in a small portion of the rabbits. Specific precipitation could be intensified and hastened by lipoids. As lipoids might also intensify the antigenic effect of proteins, rabbits were given injections of mixtures of alcoholic extracts of meat and lipoids. Antiserum with a titer of 1:20,000 were obtained in 94 per cent of the animals. Thorough immunization of rabbits with serum and heterologous lipid antiserum fit for use could be produced in only about 50 per cent. To exclude the effect of lipid in the injected serum, the serum was treated with ether. The use of such purified serum did not always prevent the production of nonspecific precipitins. Good results were obtained with dried serum after removal of the lipoids by alcohol extraction. Dried serum thus treated combined with heterologous lipoids produced in general more species-specific precipitins than dried serum with homologous lipoids.

W C HUEPER

PREVENTIVE IMMUNIZATION AGAINST CHOLERA WITH TOXOIDS R KRAUS and N KOVACS, *Ztschr f Immunitätsforsch u exper Therap* **55** 316, 1928

The injection into rabbits and guinea-pigs of cultures of cholera vibrios to which a diluted solution of formaldehyde USP (1:0.5) has been added at 37 C, induces resistance to cholera toxins and cultures. Such cholera toxoids proved harmless to persons who responded by producing cholera agglutinins.

W C HUEPER

THE SEROLOGIC REACTIONS OF EXTRACTS OF TAPEFWORMS H SACHS and A KLOPSTOCK, *Ztschr f Immunitätsforsch u exper Therap* **55** 341, 1928

Water extracts of tapeworms, when injected into rabbits, lead to the formation of protein and lipid complement-fixing antibodies. Alcohol extracts of tapeworms are antigenic only when they are first mixed with protein, as hog serum, in which case the resulting antisera give strong reactions for the lipid. These antisera also react with other organ lipoids, but not with lecithin. A lecithin antiserum, however, reacts with the tapeworm extract. The tapeworm extract is thus considered to contain specific as well as nonspecific lipid antigens.

ARTHUR G COLI

THE IMMUNITY OF SYPHILIS IN RABBITS P UHLFENHUTH and H GROSSMANN, *Ztschr f Immunitätsforsch u exper Therap* **55** 380, 1928

A spontaneous cure in rabbits from syphilis does not seem to occur. The disease becomes only latent. This conception is supported by the negative result

of a testicular reinfection and the positive results from inoculation with lymph nodes and tissue of other organs of infected animals. Infected rabbits treated in an advanced stage with neosilver arsphenamine and atoxyl acid bismuth showed the existence and the persistence of an active immunity in spite of any evidence of a latent infection as demonstrated by the negative inoculation of other animals with lymph nodes and by the negative result of testicular reinfections. Immunization against syphilis is a slow process as animals are susceptible to reinfection during an early stage of the disease. During the later stages the spirochetes adapt themselves to the immune organism. Animals cured at an early stage by chemotherapy are susceptible to reinfection. The antibodies against spirochetes are mainly bound to the cells. The results in rabbits cannot be applied without modifications and restrictions to syphilis in human beings.

W C HUEPER

THE FERMENTOCYTIC [LIPOLYTIC] REACTION OF THE ORGANISM M J  
AKSJANZLW, *Ztschr f Immunitätsforsch u exper Therap* **55** 423, 1928

Rabbits and guinea-pigs after injection of neutral fats presented a lymphocytosis, occasionally reaching 95 per cent, an increase of the lipolytic index of the serum, and after a brief temporary decrease during the negative phase an absolute leukocytosis reaching 30 per cent in some cases. The lipolytic ferments are apparently freed on the decomposition of the lymphocytes. The introduction of substances not containing lipoids do not produce lymphocytosis and increase in the lipolytic ferments, rather a decrease. Rabbits with high lymphocytosis and lipolytic index anesthetized with ether, a lipolytic substance, show a rapid increase in the lipolytic ferments and a simultaneous decrease of lymphocytes. The author asserts that in diseases showing an active reaction of the lymphopoietic organs the lipolytic ferments and the lymphocytes play an important part and are of diagnostic, prognostic and therapeutic significance. The fat and lipid therapy of tuberculosis is referred to in this connection. Lymphocytes are apparently destroyed by the introduction of fat soluble substances as ether, because degenerated lymphocytes were seen in the blood after such procedures.

W C HUEPER

THE SKIN IN IMMUNITY E URBACH, *Ztschr f Immunitätsforsch u exper Therap* **55** 471, 1928

The nonspecific reactivity of the skin, that is its quality to produce nonspecific antibodies, is the result of a phylogenetic adaptation. This function is used therapeutically (sun, water, air-baths, massage, etc). The specific allergy of the skin is usually due to an acquired specific sensitization. There exist close relations between both, as a strong nonspecific reactivity increases the specific defensive forces of the skin. The specific allergy of the skin depends on the formation of specific cutaneous antibodies. They were demonstrated by other authors by successful passive transmission of the cutaneous hypersensitiveness (graft of sensitized skin, injection of serum of cutaneous vesicles). The latter method is regarded as superior to the blood serum method of Prausnitz-Kustner as the specific character of this test is considered as dubious. The demonstration of specific cutaneous antibodies explains the diagnostic value of the cutaneous reactions and the success of those therapeutic procedures in which living virus of lowered vitality is introduced as an antigen into the most superficial layers of the skin. The employment of the percutaneous method in favor to the intradermal one is recommended for diagnostic and therapeutic purposes. Its advantages consist in simpler technic, less subjective symptoms, no anaphylaxis, almost no local reaction and especially the use of the production of specific and nonspecific epidermal antibodies. Epidermis (Langhans' cells) and cutis (vascular endothelial cells) possess the quality to form antibodies. The constitutional disposition of the epidermis and papillary vessels respectively, and not the chemical character of the antigen determine the place of action of the allergen.

W C HUEPER

THE EFFECT OF CYTOTOXIC ANTISERUM IN VITRO R. KIMURA, *Ztschr f Immunittatsforsch u exper Therap* **55** 501, 1928

Rabbits treated with tissue pulp of chicken embryos produce a cytotoxin against chicken cells. When such antiserum is added to cultures of embryonal and adult cells of chicken, it inhibits their growth. The presence of a complement is not necessary for this action. Heat and storage impair its efficacy. It is species-specific as it does not act on cells of rabbit and mouse, and it is almost organ-specific after injection of brain pulp.

W. C. HUEPER

THE ETIOLOGY AND PATHOLOGIC ANATOMY OF REACTIONS AFTER TRANSFUSION OF BLOOD ARVID LINDAU, *Acta path et microbiol Scandinav* **5** 382, 1928

This article gives a review of the literature on unfavorable reactions following transfusion, with reports of three illustrative cases studied by the author. The severe reactions depend on the transfusion of incompatible blood followed by hemolysis. The principal lesions develop in the kidneys and liver, and in certain cases also in the intestine. The lesions in the kidneys and the necroses in the liver are microscopically characteristic.

PNEUMOCOCCUS IMMUNIZATION BY INTRATRACHEAL ROUTE H. NAKAJIMA, *Scientific Reports Government Instit Inf Dis* **6** 97, 1927

Successive intratracheal inoculation of rabbits with killed or live pneumococcus cultures produced agglutinins of low titer in the blood. Rabbits thus immunized are protected from pneumococcus septicemia when virulent organisms are injected intravenously, but are not protected against pneumonia.

E. P. JORDAN

ON THE FORMATION OF ANTIBODIES BY MIXED IMMUNIZATIONS K. TANAKA, *Scientific Reports Government Instit Inf Dis* **6** 119, 1927

Experiments with mixed immunization using two different bacilli indicated that the antibodies of both were increased. But antibodies to cholera bacilli were diminished by attempted immunization with cholera bacilli and horse serum.

E. P. JORDAN

ON THE ANTIGENIC SPECIFICITY OF EPITHELIAL CELLS K. TANAKA, *Scientific Reports Government Instit Inf Dis* **6** 139, 1927

The author supplements his previous work on tissue specificity concluding as a result of his experiments that lung tissue is serologically close to spleen and different from liver, muscle tissue, and the mucosa of the alimentary tract. He also concludes that the stomach mucosa and the testicular tissue have a high degree of organ specificity.

E. P. JORDAN

## Tumors

PRIMARY MULTIPLE HEMANGIOMA OF THE SPLEEN WITH MULTIPLE LIVER METASTASES ARTHUR W. WRIGHT, *Am J Path* **4** 507, 1928

There is here described a case of primary malignant hemangioma of the spleen which metastasized to the liver, with the production of innumerable tumor masses in that organ. The type cell is the endothelial cell, and the tumor and its metastases are characterized by the formation of blood vessels and blood-filled spaces. The latter are of atypical and unusual appearance. They exist as small or large, cystlike vascular cavities into which they project varying numbers of remarkable papillary processes which are covered with rapidly growing endothelial cells. These processes differ from any structures previously described. Neoplastic growth in these foci is active, malignant and invasive. Alternating with the regions of rapid

and atypical growth there are other foci in which typical blood vessel formation is more evident. Here neoplastic activity is diminished or quiescent, and marked sclerosis is present. In these areas the growth assumes the form of fibrosed hemangiomas. The tumor is remarkable for its rapid, invasive growth, its unusual histologic structure and the formation of multiple metastases. A review of the literature concerning other cases of malignant, metastasizing hemangioma is given.

## AUTHOR'S SUMMARY

PRIMARY CARCINOMA OF THE LIVER TWO CASES IN CATTLE WILLIAM H. FELDMAN, *Am J Path* **4** 593, 1928

From a review of the literature one must conclude that primary carcinoma of the liver is not one of the common tumors of the lower animals. Of the domesticated species the dog seems to be the most often affected. The tumors have also been reported in the following species: horse, cattle, sheep, cat, hog, woodchuck and chicken. In one series reported by Trotter, 119 cases were found in 39,704 necropsies on cattle. The true primary carcinoma of the liver arises from the parenchymatous hepatic cell, and while the tumor is occasionally extremely malignant, it usually exerts its major influence on the hepatic substance in which it arises, metastasis being the exception rather than the rule. Two original cases of primary carcinoma of the liver are reported, both occurring in cattle. Metastasis was not observed in either case.

## AUTHOR'S SUMMARY

ADENOMA AND CARCINOMA OF THE THYROID FREDERICK A. COLLIER, J. A. M. A. **92** 457, 1929

Endemic goiters developed carcinoma in 4 per cent. In most of the cases the carcinoma was not suspected before operation. Of 90 cases, 28 per cent concerned medullary carcinoma, 66 per cent adenocarcinoma and 5.5 per cent scirrhous carcinoma.

THE NATURE OF THE CARCINOGENIC AGENTS IN MINERAL OILS C. C. TWORT and J. D. FULTON, *J Path & Bact* **32** 149, 1929

In fractional distillation of carcinogenic oils the active agent is sometimes concentrated in the higher, sometimes in the lower fraction. The active agent is concentrated in extracts made with methyl sulphite or methyl sulphate and picric acid, and the process is useful in testing oils intended for industrial use. There is no evidence that carcinogenic substances are made by fractional distillation or by the processes of extraction used. The carcinogenic activity of an oil is much reduced or completely removed by extraction with sulphuric acid, by oxidation and by reduction.

## AUTHORS' SUMMARY

OBSERVATIONS ON INTRACEREBRAL GRAFTS OF HOMOLOGOUS AND HETEROLOGOUS TUMORS E. HARDE, *Ann de l'Inst Pasteur* **42** 1259, 1928

Of twelve susceptible rats, grafts into the brain of a homologous sarcoma gave ten positive results. A series of rats of a race naturally refractory gave practically no positive results with a rat tumor. Nineteen white mice gave sixteen positive results with a mouse sarcoma. A mouse sarcoma grafted on seven susceptible rats gave four tumors. The same tumor on fourteen rats gave seven successful grafts. A mouse tumor was implanted on a guinea-pig one time out of six. "The rarity of stroma in the tumor at the end of its development, the absence of conjunctival capsule, the abundance of vessels, some areas of necrosis and sometimes the presence of a strong lymphocyte and perivascular reaction in certain points of the periphery of the heterologous grafts or else in the cases of resistant animals, finally the lymphocyte perivascular cylinders at a distance from the tumor" were noted microscopically.

## FROM THE AUTHOR'S SUMMARY

THE PRESENT DAY ORIENTATION ON THE IDEAS OF CANCER SOME DISPUTED POINTS ON THE ETIOLOGY OF CANCER TISSUE CULTURES AND THEIR APPLICATION TO THE STUDY OF CANCER LEAD IN THE TREATMENT OF CANCER, THE FREQUENCY OF CANCER AFTER RECENT MORTALITY STATISTICS G ROUSSY, R LEROUX, M WOLF, A HERAUX and SIMONE LABORDE, *Ann de med* **24** 345, 396, 411, 419, 1928

The enumerated articles represent a scholarly review and a discussion on the problems of cancer as they stand at the present time

B M FRIED

CONCERNING THE SARCOMA OF ROUS AND RECENT EXPERIMENTS BY CARREL H T DEELMAN, *Ann de med* **24** 360, 1928

Carrel stated that he was able to cause a new growth by injecting into a chicken a mixture of arsenic with the chick embryo pulp Deelman failed to repeat Carrel's experiments He then reports his experiments with mixture of Rous' sarcoma and embryonic pulp Here he was able to corroborate observations made by others that such a combination increases the malignant power of Rous' virus He believes that the "cellular juice" are responsible for this phenomena, the virus of Rous is attracted by the living embryonic cells thus freeing the fluid from it In a living animal things happen then in this way the "agent" of Rous which is able to "multiply" outside of the cell is attracted by the living cells When the neoplastic cells undergo necrosis the virus becomes free and contaminates the surrounding healthy cells The tumor grows rapidly because of the rapid division of the cells

B M FRIED

DEVELOPMENT OF ADENOCARCINOMA OF RATS VARIOUSLY TREATED G MENDOLA and C LORETO, *Tumori* **2** 549, 1928

On the basis of experiments the authors conclude that the antiblastomatic action of autolysates and of extracts of homologous tumors is not destroyed by ultrafiltration through a Chamberland L' filter They did not find any specific antiblastomatic immune bodies in the serum of rats that carried tumors

W OPHULS

THE CONNECTIVE TISSUE TUMORS OF THE ABDOMINAL WALL ONOFRIO ANGELELLI, *Tumori* **2** 594, 1928

Six cases of fibroma and fibrosarcoma of the abdominal wall are described with review of the pathogenesis, the pathologic anatomy, the symptomatology, the differential diagnosis, the prognosis and the treatment of these tumors

W OPHULS

ANTIBODY FORMATION AGAINST INOCULATION CARCINOMA IN THE MOUSE K YAMAGIWA, S TSUKAHARA and S MORIMOTO, *Virchows Arch f path Anat* **267** 17, 1928

The authors were able to show that growth of inoculated carcinomas in mice could be inhibited by injecting extract of spleen from rabbits which had been previously treated with emulsion of mammary carcinoma from mice In some instances, retrogression of a preexisting tumor took place This discovery indicates the formation of an antibody for mammary carcinoma of mice in the spleen of rabbits treated with an emulsion of the corresponding tumor The activity of the splenic extract was much diminished after two weeks, and so had to be freshly prepared

B R LOVETT

EXPERIMENTAL PRODUCTION OF TERATOMAS OF THE TESTIS IN THE COCK I MICHALOWSKY, *Virchows Arch f path Anat* **267** 27, 1928

There are two main theories of the origin of the solid teratomas found in the ovary or testis, and containing embryonic tissue from all three germ layers According to the blastomere theory, the tumor arises from a blastomere split-off

during the early development of the organism. According to the theory of Wilms, Pfannenstiel, and others, cells of the sex glands have the power of developing these tumors. The author injected 5 per cent solution of zinc chlorate into the testicles of cocks, and in this way was able to produce typical teratomas 9 times out of about 200 operations. The tumors were found from two to three months after injection. Other conditions necessary for the development of the tumors could not be determined, but a transitional stage occurred in which collections of cells of the sperm-forming type were observed lying between the canals. The setting free of these cells into the interstitial tissue and their growth there seemed to be a *sine qua non* for the tumor formation. The author concludes that the sperm cells of the cock, like egg cells, have the power of growing into different kinds of tissue under certain conditions. His results favor the theory of growth of teratomas from the sex gland elements.

B R LOVETT

### Medicolegal Pathology

BACTERIOLOGY IN CONNECTION WITH FORENSIC MEDICINE ROBERT DONALDSON, *J State Med* **36** 497, 1928

There is a period elapsing between death and the onset of putrefactive changes during which pathogenic organisms that may have established themselves in the blood may be recovered in culture, if suitable precautions are taken. This period, under average mortuary conditions, in temperate climates may be as long as thirty-six, forty-eight or more hours post mortem. The blood should be collected from one of the peripheral veins, preferably from the femoral, before the body is opened and, in addition, from the right and left sides of the heart. Such bacteriologic examinations may yield information of considerable medicolegal value concerning the cause of death, especially in cases of sudden or unexpected death and in cases in which, during life, the diagnosis has been obscure. It is of further value in that it may throw fresh light on the mechanism by which death was brought about, especially when chronic disease was known to exist.

AUTHOR'S SUMMARY

GLASSBLOWERS' CATARACT H ERGGELET, *Ber u d 46 Zusammenkunft d deutsch ophth Geselsch* **46** 234, 1927

The eyes of 131 laborers in the glass factories of Jena and Ilmenau were examined. In three, minimal opacities, punctiform and minute foci like soap suds in appearance, were found in the polar regions of the lenses. The only real cataracts were in two laborers already pensioned. Only 37 of the 131 laborers were over 45 years of age. Another factor in the low incidence of cataract was the absence of green glass, among the products manufactured. Green glass is said to be especially productive of cataracts.

E R LE COUNT

UNUSUAL CORONARY OCCLUSIONS G SCHMIDT, *Deutsche Ztschr f d ges gerichtl Med* **11** 380, 1928

The left coronary artery is more commonly obstructed when abrupt death results from lack of sufficient blood to the heart muscle from occlusion of the coronary arteries. Two sudden deaths in persons apparently well are reported by Schmidt, both from plugging of the right coronary artery at its mouth. In one, the obturating mass was a polypus clot washed in during diastole. From an inflammation of the aortic valves, a mural endocarditis of the aorta by implantation had developed. Subsequently the valvular process had healed, and a polyp of partly organized fibrin remained attached to the lining of the aorta root. The free end of this finally was carried into the mouth of the right coronary artery and blocked it firmly.

The other death was similar, but the polyp was fast to one of the aortic leaflets, and the free end was carried into the mouth of the artery during systole.

E R LE COUNT

DEMONSTRABLE DISEASE OF THE BRAIN IN EXHUMED BODIES W WEIMANN,  
*Deutsche Ztschr f d ges gerichtl Med* **11** 388, 1928

Embalming of the dead is uncommon in European countries. As a consequence the changes ensuing in, and the conditions which determine postmortem decomposition, as well as the information which can be obtained by examining bodies in varying stages of putrefaction, have been subjects of frequent comment in foreign journals of legal medicine. It has been ascertained, for example, that the connective tissue stroma of organs resists decomposition for a long time, that epithelium of all sorts quickly disintegrates, especially if highly differentiated, and that putrefaction in the brain is slow. This last-mentioned fact is believed to be due to the large quantity of lipoids in the brain.

There is one record of maintenance of the contour of the brain in a body after thirty-seven years of burial. Gross lesions such as contusions, apoplexy and sclerosis of cerebral vessels are easily found, although not invariably, long after death. The myelin sheaths of nerves and ganglion cells are easily found microscopically even when the brain is semifluid from decomposition. Ganglion cells have been found scattered about on surrounding objects as a result of crushing injuries of the head, long after the tissue has dried. They have also been found after the brain tissue has been burned or desiccated with heat.

Fischer, in Prague, experimenting with the brain tissue of patients with senile dementia and general paresis, found characteristic changes microscopically when the material had been kept from two to three weeks at 12 to 14 C. The report by Weimann is similar. The lesions of paresis were demonstrated in a brain twelve days after death, the organ having been put into formaldehyde promptly at the time of exhumation. Of course, when bodies are embalmed before burial, a microscopic examination of the brain is always essential, even though exhumation is months or years after burial.

E R LE COUNT

TRAUMATIC INTRACRANIAL LACERATION OF NORMAL VERTEBRAL ARTERIES  
 K WOLFF, *Deutsche Ztschr f d ges gerichtl Med* **11** 464, 1928

During recent years there has been gradual acceptance of the view that traumatic intraleptomeningeal and subdural hemorrhage of venous origin may occur without either fracture of the cranial bones or bruising of the brain, also that such hemorrhages may cause death quickly. The brain is frequently so covered with blood that the convolutions are almost invisible. The actual site of bleeding is not found, as a rule. Fatal hemorrhages of this kind are not uncommon.

Similar traumatic hemorrhages from traumatic lacerations of large intracranial arteries also occur, but they are rare. They also may happen without contusion of the brain or fractured bones. There are only about four reports of such occurrences. Wolff reviews them all briefly and adds one case from his own experience. In some of the cases there are ruptures of the basilar artery, in others of the vertebral artery and in one, that of a man, aged 71, there is a torn pial artery. One of the basilar tears, incomplete, was 7 mm long, the adventitia was intact, the artery channel thrombosed and the wall free from disease. In another case there had been hypertrophy of the heart which weighed 470 Gm, increased blood pressure may have played a role. Death takes place quickly when the tear is all the way through the vessel wall. The hemorrhage spreads around the outside of the brain distends the fourth ventricle and extends into the other ventricles.

Where the vertebral arteries emerge from the atlanto-occipital membrane they are fixed firmly. Crossing the subdural loose tissues of the leptomeninges, they come to lie against the rigid clivus of the occipital bony plate. It is believed that falls which turn the head suddenly to one side may kink the vertebral or basilar arteries in these portions of their course where they lie relatively free, the walls are torn by compression by bone outside, and the incompressible fluid inside is unable to move along in the channel because the vessel is kinked. The



tears, moreover, are ventral. It will be recalled that trauma has been offered as an explanation for aneurysms of these vessels. It has been suggested that the basilar artery, for example, may be bruised against the edge of the foramen magnum.

E R LE COUNT

POISON STATISTICS E R GRAWITZ and A WAEGER, *Ztschr f klin Med* **106** 783, 1927

This is a second summary of the poisonings cared for in a single hospital in Berlin. The first appeared as an inaugural dissertation by Beeck in 1925, "Ueber klinische Beobachtungen bei Leuchtgasvergiftungen." In the period covered by the two reports, about fourteen years, the total number of cases of poisoning was 1,135, of these, 842 were due to carbon monoxide. The mortality is not mentioned. Among 703 of the 1,135, there were 331 attempted suicides, 242 by women and 89 by men, only 43 were successful, and 146 were by persons between 20 and 30 years of age. Of 77 poisonings by veronal, only 3 were not suicidal.

The list of alkaloidal poisons, or of poisons with names suggesting alkaloids, is a long one and includes barbitol and barbitol derivatives, revouerin, dihydrocodeine, pantopium hydrochloricum, quinine, acetyl-salicylic acid and carbonal. It is of interest that no difficulty apparently exists in obtaining these rather unusual drugs when they are desired for suicide, and also that they are responsible for accidental poisoning.

E R LE COUNT

### Technical

A NEW SELECTIVE STAINING METHOD FOR THE DEMONSTRATION OF THE GLOMERULAR VASCULAR BED STUART WILSON, *Warthin Ann* Vol, 1927, p 519

After experimenting with a number of dyes, Wilson considers that a distilled water solution of janus green (1:800) injected into the renal artery after perfusion with physiologic salt solution, gives the best stained preparations of the glomerular-vascular structures. Frozen sections, not cleared, but air dried and mounted in balsam give best results. The method is applicable to kidneys removed surgically, autopsy material and experimental investigations in animals.

WALTER M SIMPSON

A NEW SYPHILIS REACTION (MKR) E MEINICKE, *Klin Wchnschr* **8** 112, 1929

Meinicke offers another flocculation test for the serum diagnosis of syphilis. For the details of the procedure the original article should be consulted.

EDWIN F HIRSCH

REPLACEMENT OF THE SKULL OF THE CADAVER BY A WAX MODEL L PICK, *Virchows Arch f path Anat* **266** 604, 1927

A method is described for substituting a wax model instead of a plaster one for the skull of the cadaver. This makes a more lifelike appearance possible.

B R LOVETT

A SELECTIVE STAINING METHOD FOR BROWN AND MELANOTIC PIGMENTS E P LASNIER, *Virchows Arch f path Anat* **266** 693, 1928

A method (see the original) is described for staining brown pigment, especially in the muscle of the heart, and melanotic pigment in the skin and in tumors. The method enables clear distinction between these and other substances, such as iron-containing blood pigment and bile pigments, which may have the same appearance with ordinary staining methods.

B R LOVETT

# Society Transactions

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## CHICAGO PATHOLOGICAL SOCIETY

*Regular Monthly Meeting, Dec 10, 1928*

HENRY C SWEANY, *Vice-President, in the Chair*

### BLOOD CHANGES IN MECHANICAL CONSTRICTION OF THE HEPATIC VEINS W W BRANDES and J P SIMONDS

Two years ago we devised a method of mechanically constricting the hepatic veins in the dog. Briefly stated, this consists in passing a small sized rubber tube through the foramen of Winslow and through the ligamentous attachments of the liver taking care to include all the lobes. The two free ends of the tube are brought up over the surface of the liver and passed through two small holes bored lengthwise in a small flat wooden block. By pulling up on the ends of the tube and at the same time pushing the block downward the hepatic veins can be constricted to any desired degree up to complete obstruction. By placing a clamp on the rubber tube immediately above the block the inferior vena cava is not at all interfered with. By this method the liver can be shut out of the general circulation and returned at will.

The changes in blood pressure induced by this procedure consist of a precipitate fall in arterial pressure of from 40 to 60 mg of mercury. The pressure reaches a level which is reasonably constant for at least twenty minutes. On release of the hepatic veins, the blood pressure rises immediately to a level usually about 10 mm higher than before constriction and returns to normal in about one-half minute. This marked fall in arterial pressure is due to the sudden throwing out of the general circulation of the large volume of blood in the liver and branches of the portal vein.

Along with this decrease in blood pressure the flow of lymph from the thoracic duct is markedly increased, an average increase of 52 times normal.

Determinations of blood concentration by the method of Lamson and Roca show that a rapid moderate dilution of the blood occurs during the first five minutes of constriction followed by a gradual recovery during the following ten minutes before the hepatic veins are released. The marked increase in flow of lymph from the thoracic duct, and the entrance of fluid into the blood from the tissues as is the case in low blood pressure from hemorrhage are probable factors in this dilution. The reason for the gradual return of concentration to normal is not clear. It may be due to the forcing of a small amount of highly concentrated blood through the constriction as a result of the increased pressure in the liver and to the fact that the lymph in the thoracic duct usually shows red blood cells after the first five minutes of constriction.

The coagulation time in these animals before constriction ranged from two and one-quarter to four and one-half minutes. Constriction of the hepatic veins caused a distinct shortening of the coagulation time, from an average in six dogs of two hundred and ten seconds before constriction to an average of ninety seconds, ten minutes after constriction was applied. No clear explanation is offered for this change, and further studies are being made to determine its cause. It may be that the heparin of the blood is rapidly used up, thus allowing coagulation to occur more readily. There is no satisfactory quantitative test for heparin in the blood. A number of determinations on the quantity of fibrin have been made but as yet not of sufficient number to justify any statement, but there seems to be a decrease when the hepatic veins are constricted. Blood platelets also show a tendency to decrease apparently. Work is to be carried out on calcium and  $pH$  determinations.

Mann and others have shown that total removal of the liver results in a fall of blood sugar to such a low level that hypoglycemic convulsions occur. Constriction of the hepatic veins results in a surprisingly rapid fall in the blood sugar. There was an average maximum fall of 42 per cent in fifteen minutes after constriction. As soon as the constriction is released the blood sugar promptly rises to a level considerably higher than that before the veins were constricted. We believe that the marked congestion and stasis in the liver causes a local acidosis which stimulates glycogenolysis, thus liberating sugar in the liver. When the hepatic veins are released, there is delivered to the general circulation a hepatic blood with a high concentration of sugar. We tested several dogs by starving and insulin injection to render the liver glycogen-free. In these the constriction of the hepatic veins caused only slight fluctuations in blood sugar.

## DISCUSSION

E F HIRSCH Have measurements been made of the reaction or carbon dioxide combining power of the blood?

W F PETERSEN I have blocked the liver by injecting petroleum into the portal vein, and in twenty minutes noted liver injury. The lymph from the thoracic duct at first was thin, later concentrated. The carbon dioxide combining power at first was increased but later diminished, and some bile appeared in the lymph. Was the concentration of the bile determined?

J P SIMONDS Further studies in answer to the questions asked are in progress.

## PRIMARY INTRAHEPATIC THROMBOSIS OF THE PORTAL VEIN LOUISA HEMKEN BACON

Most of the reports in the medical literature of the thrombosis of the portal vein which accompanies atrophic cirrhosis of the liver, refer to its origin and subsequent development outside the liver in the large trunk or its right and left branches, and to an extension of the thrombosis out into the liver (Webster, L T Portal Thrombosis, *Bull Johns Hopkins Hosp* 32 16, 1921, Quincke, H, and Hoppe-Seyler, G, in Nothnagel Encyclopedia of Practical Medicine, Diseases of the Liver and Pancreas, and Suprarenal Glands, Philadelphia, W B Saunders Company, 1905, p 885). The study I have made is apparently of a contrary course of events, a retrograde thrombosis in the branches of the portal vein from many places far out in the peripheral parts of the liver to the extrahepatic main stem which became secondarily occluded shortly before death.

The patient, a woman, aged 61 years, was admitted to the service of Dr Lester E Frankenthal, Sr, in the Michael Reese Hospital, Chicago. The only noteworthy information regarding her previous health was that following the birth of a healthy normal child when she was 39 years of age, her physicians said she had, for a time, suffered from uremia. On admission, she complained of enlargement of the abdomen, dyspnea and cough. The enlarged abdomen was tense so that abdominal organs could not be palpated. The blood count was within normal limits. A trace of albumin was present in the urine, and occult blood was found in the stools on two occasions, on the day of admission and two days later. Examination of the blood revealed 115 mg of sugar per hundred cubic centimeters, 37 mg of nonprotein nitrogen and 1.3 mg of creatinine. While under observation and treatment in the hospital for eighty-two days (until death), there was a slight fever during the afternoon (99.4 to 100.8 F) for the first two weeks, during the following three weeks there was some fever all the time (99.2 to 100.4 F), being highest in the afternoon. This increased to from 100 to 103 F, falling only slightly for a short time after the second operation. During the last two days of life, the temperature never went below 102 F, and reached a maximum of 105 F a few hours before death.

Fluid was removed from the abdomen 8, 36, 37, 52 and 72 days after admission. On the thirty-seventh and fifty-second days, it was obtained at the time of opera-

tions Altogether  $8\frac{3}{4}$  gallons of a milky fluid were removed The largest amount at the last tapping on the seventy-second day was  $2\frac{1}{2}$  gallons, the smallest, at the time of the first operation, was 1 gallon Fifteen days after admission a diagnosis of sarcoma of the mesentery was made from examination of a small piece of tissue which came away in the fluid

Exploratory laparotomy was performed thirty-seven days after admission the omentum was indurated, the liver was atrophic and the peritoneal covering of the small bowel was studded with engorged blood vessels No tumor tissue was found in the fluid removed at this operation Epiplopexy was done fifteen days later, two days later slight cyanosis and dyspnea were observed There was a persistent thick discharge from the incision made during the recent laparotomy Eighteen days after the operation air hunger and marked tightness of the abdomen were present Coma, involuntary passage of urine and watery feces were observed during the last few days Death occurred twenty-nine days after the second operation The clinical diagnosis was cirrhosis of the liver with terminal uremia

The anatomic diagnosis, made by Dr E R Le Count was primarily intrahepatic retrograde thrombosis of the portal vein, atrophic cirrhosis of the liver, marked shortening (cyanotic induration) of the small bowel, marked dilation, tortuosity and engorgement of the blood vessels of the peritoneum compensatory to the obstructed portal circulation, chronic indurative epiploitis, recent epiplopexy, two recent laparotomy incisions, stitch-abscesses in the subcutaneous fat of the abdomen, hyperplasia of the spleen, markedly distended abdomen, anasarca, slight bronchopneumonia, disseminated superficial atelectasis of the lower lobes of both lungs, bilateral hydrothorax, fatty changes of the kidneys, cloudy swelling of the kidneys and myocardium, minute hemorrhages in the diaphragm, and mucous membranes of the stomach, bowel and renal pelvis, and senile arteriosclerosis

The disease of the liver was typical portal cirrhosis It was evident from its external appearance that the main branch of the portal vein was thrombosed, for the vessel had a round plump contour The clot in it was 5.4 cm in length and about 1 cm in diameter, forked slightly at the mouths of the splenic and mesenteric veins and adherent ventrally When detached, a gray spot only a few millimeters in diameter was found in which the vein had lost its normal sheen The clot was easily followed out into branches of the right lobe of the liver until the channels were not more than 2 mm in diameter It did not extend into the left lobe

Because the thrombus in the main vein possessed all the characteristics of recent formation and the removal of large amounts of fluid from the abdomen had been carried out at rather frequent intervals, a microscopic study was made to learn whether thrombosis of the small branches of the portal vein was generalized throughout the liver Sections were studied from eighteen places, and partly organized thrombi were found in those from four places in the right and one in the left lobe Those from the right were 2.6, 4, 7 and 8 cm, respectively from the upper surface, that from the left was 3.6 cm below The most peripheral branch thrombosed in these sections was a small vein with a channel from 0.075 to 0.37 mm in diameter This was from the piece removed 2.6 cm below the upper surface of the right lobe The organization in this branch was more marked than in any of the intrahepatic veins found occluded The clot in a larger branch 7 cm below the upper surface of the right lobe was bound fast by considerable granulation tissue at three places in sections obliquely through the vein where the diameter of the channel was from 4 to 7 mm No clots were found thoroughly organized in any of the sections of the liver

In the preparations from the large extrahepatic thrombus altogether about 14.3 cm of contact of thrombus and intima were examined microscopically, and only the earliest changes of fibroblast invasion were found These occupied only about one twenty fifth of the total junction between clot and vein, and the deepest invasion of the clot was a small triangular mass of fibroblasts and vessels projecting into the clot for a distance equal to only one fourth of the width of the wall of the vein

In the most peripheral branch of the portal vein containing an organized clot, already described, and with a channel from 0.075 to 0.37 mm in diameter, the wall is from 0.225 to 0.313 mm in width. Its adventitia consists of heavy collagen fibers (the sections were stained with phosphotungstic acid hematoxylin) and make up from one half to two thirds of the entire wall of the vein (figure). These are arranged transversely and merge with similar fibers in the outer coat of the adjacent hepatic artery. At other places it appears as if these fibers have pushed



Portal vein containing a thrombus in the right lobe of the liver (from a region 2.6 cm below the superior margin). 1 indicates fibrin, 2, fibroblasts surrounding fibrin, 3, place of adherence of clot, 4, intima, 5, media, 6, adventitia (collagen fibers), 7, interlobular stroma,  $\times 133$

aside the interlobular fibro-elastic stroma so that there is little of the stroma between the liver cells and portal vein. Definite elastic fibers are between the adventitia and media, the media has smooth muscle and elastic fibers and is from one half to one third of the width of the portal vein. The intima is not thickened.

In the other intrahepatic branches of the portal vein there is a similar change. In some the media has become much narrowed, and the adventitia is particularly wide and prominent. In each section studied from the eighteen different places in the liver, the walls and channels of one or more portal veins were measured. The ratio between the width of the wall and the diameter of the channel was usually 1:1, in a few 1.5:1, and in some of the larger branches 1:4. The channels are narrow compared to the width of the walls. In some veins there are (figure) places in which the wall attains a greater width than the diameter of the channel, in many the two are the same.

The wall of the extrahepatic portion of the portal vein is from 0.125 to 1.20 mm thick. The adventitia has collagen fibers, but these are not so densely arranged as in the walls of the intrahepatic branches, here they are separated by loose areolar tissue.

The bile ducts about the large intrahepatic branches of the portal vein are heavy due to circularly arranged collagen fibers. They form a broad band about the epithelium of the bile passages about the same width as the adventitia of the adjacent portal veins, in a few they are even greater, reaching a maximum of from 0.4 to 0.5 mm.

The portal cirrhosis was of long standing and was the primary disease. Sclerosis of the portal vein may accompany atrophic cirrhosis (Simmonds, M. Ueber Pfortadersklerose, *Vnchows Arch f path anat* **207** 360, 1912), the intima is usually much thickened, the media may be wider than normal, and often its elastic fibers are torn. The outstanding characteristic of the thickened portal vein of this report is the marked thickening of the adventitia. This would suggest, together with the thickened walls of the bile duct, that at some time there had been a lymphangitis extending into the liver from the adjacent structures, with subsequent healing and the laying down of collagen fibers about the bile ducts and in the outermost coat of the portal veins within the liver. Syphilis is ordinarily considered to be the prime etiologic factor in sclerosis of the portal vein (Simmonds). It was definitely excluded clinically and from the gross and histologic examination of the liver.

With cirrhosis of the liver, complicated by thrombosis in the stem of the portal vein, ascites develops quickly, and the fluid is disposed to reaccumulate rapidly after tapping (Osler. Principles and Practice of Medicine, ed 10, New York, D. Appleton & Co., 1925, p. 581). In this patient, fluid collected rapidly in the abdomen when many small intrahepatic branches were occluded and before the thrombosis had extended to the stem of the portal vein. In the gross examination of the liver, the clot in the stem was followed out into branches of the large division of the portal vein for the right lobe of the liver. Histologically, the oldest and most organized clots were found in still smaller vessels with channels from 0.2 to 0.3 mm wide in both the right and the left lobes, as the portal veins become larger and closer to the hilum, the thrombi are younger in appearance. The smallest and most peripheral branches of the portal vein became occluded first, and the thrombi gradually extended into larger branches against the current. This probably took place during the four or five months just before death, finally thrombosis occurred in the stem of the portal vein, and with its formation, death soon followed. A few textbooks and recent reviews mention the occurrence of retrograde thrombosis (Stengel, A., and Kern, A. Nelson Looseleaf Living Medicine, Thomas Nelson and Sons, 1923, vol. 5, p. 521. Delafield, F., and Prudden, T. M. A Textbook of Pathology, New York, William Wood & Company, 1927, ed. 14, p. 822. Kaspar, F. Beitrage zur Kenntnis des Verschlusses im Pfortaderstamm und der Vena linealis. Kavernose Umwandlung der Vena portae und chronisches ulcus duodeni, *Deutsche Ztsch f Chir* **151** 1, 1920).

Cirrhosis of the liver usually has an afebrile course, although slight rises in temperature for short periods are observed in patients under observation for a long time (Osler). In this patient there was some fever during practically the entire ten weeks before death.

**Conclusions** From the histologic examination, it is seen that the first thrombosis occurred far out in the small branches of the portal vein within the liver, and from here extended into the stem. The branches of the portal vein are greatly thickened due primarily to a large amount of collagen in the adventitia, but the media is also thickened. The thickened walls of the bile duct consist of collagen. The deposition of collagen fibers in these two places suggests lymphangitis which may have occurred with the beginning of the cirrhosis.

#### DISCUSSION

**R H JAFFE** Thrombi such as these can be traced to the final branches of the portal vein. They are usually seen with chronic or subacute bacterial endocarditis and septicemia. The endothelial cells lining the sinusoids become swollen, and bacteria can be demonstrated in these cells. Then thrombi form, which become larger, and the process spreads toward the hilum. Similar changes occur in the spleen. Were stains or cultures made for bacteria?

**H C SWEANY** Were there changes in the hepatic veins?

**L H BACON** No stained slide preparations were made because the tissue changes did not resemble a bacterial infection. The hepatic veins were unchanged.

**NEISSERIA SUBFLAVA (BERGEY) MENINGITIS IN AN INFANT** HARRIET BENSON,  
ROSE BRENNWASSER and DOROTHY D'ANDRIA

The complete report is published in the *Journal of Infectious Diseases* **43** 516, 1928

**OSTEOGENIC SARCOMA** ERIC A FENNEL

The bone sarcoma registry classifications were discussed, and the need was emphasized for further subclassification of the osteogenic sarcomas. This group has a rather constant character, clinically, roentgenologically, surgically, pathologically and prognostically. A case was reported which must fall into this group, but which deviates in several respects from the typical.

A man, aged 45 years, with multiple exostoses (hereditary) subjected one of these to severe trauma. Within three weeks growth was noted, and in three months the size of the tumor of the femur metaphysis interfered with locomotion. In February, 1923, as much of infiltrating tumor as possible was removed and 2,400 mg. hours of radium were given. The sections contained highly cellular tumor tissue with immature cells and some bone production. A clinical recovery followed. After six years the patient is living and well. The growth seems to be an osteogenic sarcoma.

**MULTIPLE HEMANGIOFIBROMAS OF THE PULMONARY VALVE** M G BOHRD

In the body of a man, aged 20 years, dying from multiple brain abscesses, four tumors were found on a leaflet of an otherwise normal pulmonary valve. Microscopically, there were many blood vessels composed of concentric mantles of spindle-shaped cells, without division into layers, and between these there was edematous fibrous tissue and blood pigment. The subintimal elastic tissue of the pulmonary valve was intact and separated the tumors from the valve. These were considered to be true neoplasms, hemangiofibromas.

#### DISCUSSION

**R H JAFFE** These tissues are found on the valves and foramen ovale, sites in which there are islets of embryonal tissues. Are they real tumors? I think of them as "hamartomas."

**E F HIRSCH** The multiplicity of these tissues on the leaflet and the brain abscesses suggest inflammatory origin.

## PHILADELPHIA PATHOLOGICAL SOCIETY

*Stated Meeting, Jan 10, 1929*

J HAROLD AUSTIN, *Presiding*

GASTRIC ULCER IN A MONKEY (*CERCOPITHECUS CAMPBELLII*) HERBERT FOX

The specimen presented illustrates several interesting features. While numerous, small, sometimes multiple, ulcers resembling the human peptic ulcer have been encountered in the lower primates, this is the first example of puckering of the gastric wall about the defect, perigastritis with adhesions, obstruction to the antrum pylori and distortion of the duodenum, all features of considerable importance in the human histories. In addition, there was a history of the passage of blood from the mouth and nose. No source for this in the upper alimentary or in the respiratory tract was evident at autopsy, but there was to be seen a vessel end in the floor of the ulcer and there were also some tiny hemorrhages over the fundus of the stomach.

This animal, a fully adult male, had been in the collection for six and one-half years. He was exposed to tuberculosis, contracted the disease and was condemned, but died from weakness caused by the infection and hemorrhages and a generous infestation of *Subulna*.

The only observations of significant connection with the gastric ulcer are as follows. Many teeth were carious. This feature is not mentioned in the protocol of other cases of ulcers in the records. The monkey is prone to have ulcerative gingivitis and cellulitis of the facial tissues, they did not exist in the present case. Carious teeth are common.

The tuberculosis was exclusively abdominal. While the gastric wall was not subject to section, no characters of tuberculosis were seen by gross dissection. The spleen and liver, in which the tuberculous process chiefly existed, were not adherent to the stomach near the ulcer.

What effect the nematodes in the small intestine had on the gastric lesion is entirely speculative. There is one record in our laboratory in which it is evident that a worm of a similar character was coiled in the mucosa about the ulcer. No parasites were found in the stomach in the present case. The following is the description of the specimen as seen at autopsy.

"The stomach is widely distended with gas and contains only a little dull brown fluid. This distention is apparently due to a kink at the pylorus. There are very firm adhesions of the tip of the ascending colon, the omentum and the tip of the gallbladder to the pyloric end of the stomach. This was dissected away, and a scar about 2 by 1 cm exposed. On opening the stomach a ragged, sharply outlined ulcer with a gray base was exposed. This measures about 1.5 cm and its lowest extremity is just at the pyloric ring. The mucosa around the pylorus and about 1 inch above it is swollen, pink and edematous. The wall of the rest of the stomach is thin and translucent. The mucosa of the duodenum is swollen, pink and slightly eroded. Below this, the mucosa is flat, pale pink and translucent."

There was a definite ballooning of the cap of the duodenum which section has been pushed and rotated backward until it lay almost on the pancreas and aorta.

The adhesions indicated that penetration of inflammation had taken place, but that a true perforation had occurred cannot be determined. At all events the character and behavior of this ulcer are closely similar to certain occurrences in man, and the growth is the first of its kind I have seen in the wild or domestic animal.

The anatomic basis for this lesion can be the same in the monkey and in man. The micro-anatomy of the two stomachs is essentially the same. The pyloric glands of the monkey are relatively somewhat larger, and they show a greater branching near the surface than do human pyloric glands. The mucosa of the stomach of lower primates is more richly supplied with lymphatic tissue.



than is that of man, well formed follicles not infrequently being seen among the gastric tubules. Peptic ulcers of the other lower animals, though rare, are commonest in carnivores and in the abomasum of ungulates. I have never seen the partner of ulcer in crime, cancer, in the same case.

#### CHEMICAL STUDIES OF GROWTH    FREDERICK S. HAMMETT

The therapeutic use of lead in malignant disease makes imperative a determination of its action on growing organisms. The detailed report of the studies which have been made at the Research Institute of the Lankenau Hospital, of which this is an abstract, is to be found in *Protoplasma* for 1928-1929.

The test objects used were root-tips grown in culture solutions containing lead as nitrate in various concentrations. *Zea mays*, *Allium cepa* and *Phaseolus vulgaris* seedlings were used. It was found that lead is deposited in the root-tip in the region of most active cell division and that the growth in length of the roots is inhibited. The degree of inhibition runs parallel with the concentration of Pb-ion in the culture solution. Histochemical studies demonstrated that the lead accumulates within the nucleus in high concentration and also in the cell wall. Cell counts showed that mitosis is inhibited by the lead and that this occurs in greater degree the greater the concentration of Pb-ion in the culture solution. The cell size is not adversely affected. Hence, growth here is inhibited because of the inhibition of cell proliferation. It was possible to correlate lead fixation by the nuclei with mitosis, from which the conclusion seems justified that root nuclei in mitosis produce a compound precipitable by lead, and conversely that the inhibition of growth by increase in cell number is due to the throwing out of the field of action of a compound essential for cell division.

Experiments with 3 and 4 day old chick embryos showed that growth is also inhibited here. It is significant that the regions of most active growth by cell proliferation are the very regions in which differential development is most markedly retarded, namely, the head and the somites. This has been reported in the *Journal of Experimental Medicine*, 1928.

#### THE GRAPHIC METHOD FOR THE BLOOD SEDIMENTATION TEST    JACOB CUTLER

The blood sedimentation test is one of the newer laboratory procedures striving for a place as a valuable diagnostic aid and prognostic index in infectious and destructive diseases. Although known to physicians for centuries and at one time considered a particularly important clinical sign, both theoretically and practically, its present popularity is due to Fahreus, who, in 1918, introduced it as a diagnostic aid in early pregnancy. More than 650 articles have appeared in the literature since. Many of the early claims have been modified or discarded. Today, no one thinks of the sedimentation test as an early diagnostic procedure in pregnancy or in any disease entity, for the sedimentation reaction is nonspecific.

Evidence is accumulating to show that in the final analysis the sedimentation phenomenon depends on the amount of cellular destruction going on in the body. As the blood circulates from part to part, it carries away products of tissue destruction which alter its stability. In healthy persons, as a result of the wear and tear of everyday life, a certain amount of tissue destruction is always taking place, although this varies from day to day, it remains within limits considered normal. Even this relatively small amount of tissue destruction is registered by the sedimentation test.

Should the amount of tissue destruction pass beyond the normal, then the stability of the blood becomes altered and the red blood cells settle out quickly from the plasma. All the observations recorded in the recent literature emphasize this important fact: regardless of the disease present, whether it is active pulmonary tuberculosis, a malignant condition, pelvic inflammatory disease, acute infections such as typhoid fever, or any disease in which tissue destruction is going on at a greater pace than normal, the rapidity of settling of the red blood cells is in direct proportion to the severity of that disease.

It becomes evident, therefore, that the sedimentation reaction portrays a disturbed function of the blood resulting from destructive disease and should be looked on as one of the fundamental phenomena that occurs during disease and regarded as a measure of pathologic activity in the same sense as fever or leukocytosis. It is often more to be depended on than subjective or objective signs. This does not mean that the sedimentation test is to replace any established procedure or to force to the background sound clinical judgment. On the contrary, if this test is used in conjunction with a temperature chart, examination of the blood, physical examination, history and clinical judgment, it will often cast an additional ray of light on a complex problem and will promote greater confidence in the handling of the sick. The sedimentation test, therefore, should be welcomed.

Three principal methods have been developed for performing this test: the distance, the time and the graphic methods. In the distance method, one fixes the time and measures the distance through which the red cells sediment, recording the results in millimeters, while in the time method one fixes the distance and observes the time, recording the results in minutes.

The graphic method, as the name implies, expresses its results graphically and I have described it in detail in a previous communication (*Am J M Sc* **171** 882, 1926). Its essential features are as follows:

In the original technic, I used a sedimentation tube of 5 cc capacity graduated into tenths of a cubic centimeter each 1 mm in length and marked in millimeters. The graduations began with zero at the 5 cc level and increased downward to 50.

Further study, however, convinced me that within reasonable limits the quantity of blood used makes little difference. The important thing is to keep the height of the blood column constant. The utilization of this principle enabled me to perfect the finger puncture method (*Am J M Sc* **173** 687, 1927), and also makes it possible for me to present the following 1 cc technic, to which I wish to call particular attention.

The only essential apparatus required is a 1 cc Cutler sedimentation tube. This tube has an internal diameter of 5 mm and is marked in millimeters, beginning with zero at the 1 cc level and increasing downward to 50.

Before puncture of the vein, aspirate into the syringe 0.1 cc of 3 per cent freshly prepared sterile sodium citrate solution, to prevent clotting of the blood. Draw the blood up to the 1 cc mark and gently mix the blood and the citrate solution by tilting the syringe back and forth, after drawing in a little air. Pour the contents into the sedimentation tube and allow the tube to stand in the carrying rack until ready to make readings.

The test is read by noting the position of the sedimenting column of red blood cells every five minutes for one hour. This is done with ease, as the boundary zone between the red blood cells and the plasma is usually sharp and distinct. The observations are recorded on sedimentation charts, on which the horizontal lines represent the divisions on the sedimentation tube and the vertical lines the intervals of time. A graph is then constructed.

The sedimentation value is determined according to the path traversed by the red blood cells during the first hour and depends on the nature of the graph, the sedimentation index and the sedimentation time, and is the same as when the 5 cc method is used.

*Interpretation of Test*—There are four distinct graphs, two of which are straight lines, and two, curves. From their physical appearance I have named them horizontal line, diagonal line, diagonal curve and vertical curve. The horizontal line is found normally and indicates absence of active destructive disease. It does not, however, exclude the presence of such disease if it is inactive. The sedimentation test merely records the disturbance in the stability of the blood produced by the absorption of products of tissue destruction, and when there is not sufficient tissue destruction, the sedimentation test is normal. The horizontal line, therefore, may indicate one or two things: either health, or the presence of destructive disease not sufficiently active to disturb the natural stability of the blood. The diagonal

line and the diagonal and vertical curves always indicate an abnormal condition and always show the different degrees of the intensity of the destructive process

For a complete evaluation of the sedimentation test, one must determine two factors in addition to the graph namely, the sedimentation index and the sedimentation time. These bring out the finer details of the sedimentation reaction and help to determine the degree of activity or quiescence. In this way, they permit comparative study of apparently similar graphs.

By sedimentation time is meant the number of minutes that elapse before the period of packing of the red blood cells sets in. The normal sedimentation time may vary from five to fifteen hours, whereas inflammatory blood may show complete settling in less than thirty minutes. The sedimentation index is the amount of sedimentation at the end of sixty minutes, expressed in millimeters. The normal index for men varies from 2 to 8 mm, and for healthy women, from 2 to 10 mm. As already mentioned, the sedimentation index and sedimentation time help to determine the degree of pathologic activity or quiescence. The greater the index and the shorter the time, the greater is the activity, the smaller the index and the longer the time, the less is the activity.

*Advantages of the Graphic Method*—Since the sedimentation test has so many possibilities and is making such a strong bid to become a trusted laboratory aid, it is only fair to request that it should not be hampered by a multiplicity of techniques. It is hoped that the following advantages of the graphic method over those in general use will convince many who are interested in the blood sedimentation test that they should use this method.

1 It is scientific. The sedimentation reaction is studied as a natural phenomenon from beginning to end and not within the confines of arbitrary limits.

2 It is complete. It is the only method which permits of a complete study of the sedimentation reaction as it actually occurs in the sedimentation tube.

3 It is delicate. It is the most delicate method that has so far been devised. By means of the graph, sedimentation index and sedimentation time, it reveals all the possible information that the sedimentation reaction can yield.

4 The interpretation is simple. The horizontal line is found normally and indicates either health or the absolute quiescence of destructive disease. The diagonal line and the diagonal and vertical curves show an abnormal condition and always indicate the different degrees of intensity of the destructiveness of the disease.

5 It is graphic. The results are presented graphically and leave a lasting impression on the mind. Improvement or lack of improvement can be dramatically visualized by recording the data of subsequent sedimentation tests on the original chart. As the patient improves the graph should approach more and more the horizontal line, but should he become worse, the vertical curve is more and more in evidence.

6 It is time saving. No observations are made beyond the first hour. In all, only eight readings are essential.

7 It is available under all conditions. The test may be carried out by puncturing either the vein or the finger tip. Venipuncture may be done with either 5 cc or 1 cc of citrated blood. The finger puncture method requires less than 0.3 cc of blood. These methods are interchangeable, they are studied in the same manner and give practically identical results, thus making the sedimentation test available under all conditions. Of these, the 1 cc technic is the simplest and easiest.

8 It is easy. With the 1 cc technic described in this article, the sample of blood required can easily be obtained. To read the results of the test, only the average amount of careful observation is required.

#### VITAMINIZATION OF WHITE WHEAT FLOUR M. G. WOHL and F. WOOSLEY

Well marked deficiency diseases as reproduced in animals, such as beriberi and xerophthalmia, are rare in man, symptoms due to chronic vitamin B under-

feeding in man are not uncommon. Loss of appetite (Cowgill), loss of tonicity and irregularity in muscle contracture (Nelson, Balwin and Riggs) and loss of tone of the bowels (Gross) are some of the fundamental effects of food deficient in vitamin B.

The present day American diet, which consists largely of highly refined foods such as degerminated cereals, white flour bread, white rice, lean meats and sugars, has a relative shortage of vitamin B. Vegetables and fruits (cabbage, celery, cauliflower, tomatoes, apricots and apples) which are usually considered rich in vitamin B, show only traces of vitamin B when tested on pigeons. The foregoing mistaken idea has arisen through the fact that these vegetables and fruits were tested in dried form on rats. No human being eats the enormous quantities of these which would be necessary for him to obtain sufficient vitamin B (Plimmer). To enrich a widely used article of human and animal diet with vitamin B appeared a desideratum of importance. White wheat flour in the process of roller milling loses its vitamin B potency. Degerminated wheat flour does not have the tendency to become rancid. It looks whiter and bakes better. Its great biologic disadvantage is that the seat of vitamin B, the germ of the wheat grain, is removed. Experiments in feeding animals with white flour to which a concentrate of 0.5 per cent brewer's yeast was added tended to show the superiority of this over the usual white flour, as it insured constant growth in white rats and prevented polyneuritis in pigeons.

and degree of change in morphologic characters. The morphologic variations of bacteria are, therefore, an expression of the variation in growth rate.

The reviewer is not in complete sympathy with this interpretation of the data. It is admitted that the failure on the part of those who believe in life-cycles to make continuous observations of all stages of transformation is a just criticism, and, furthermore, the inability to tell whether in particular cases hypotheses or observed facts are being given is also objectionable. However, the reawakened interest in pleomorphism with the accumulation of large amounts of data by unbiased workers may soon interpret for one the real significance of morphologic variation. The book is well printed and bound, and is highly recommended to all who are interested in this fascinating subject.

## Books Received

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**PATHOLOGICO-ANATOMICAL AND CLINICAL INVESTIGATIONS OF FIBRO-ADENOMATOSIS CYSTICA MAMMAE AND ITS RELATION TO OTHER PATHOLOGICAL CONDITIONS IN THE MAMMA, ESPECIALLY CANCER** By Carl Semb From the Pathologico-Anatomical Institute of the University Hospital, Oslo Pp 484 Oslo Nationaltrykkeriet, 1928

**CHRONIC (NON-TUBERCULOUS) ARTHRITIS** Pathology and Principles of Modern Treatment By A G Timbrell Fisher Price, \$8.75 Pp 232, with 186 illustrations London H K Lewis & Company, Ltd, 1929

**REPORT OF THE INTERNATIONAL CONFERENCE ON CANCER, LONDON, JULY 17-20, 1928** Held under the auspices of the British Empire Cancer Campaign Price, \$12 Pp 588 New York William Wood & Company, 1928

This fine volume records in full the proceedings of the International Conference on Cancer in July, 1928. The contents include general discussions and papers on the etiology of cancer, the relative values of surgery and radiation in the treatment of cancer, chemotherapeutic treatment with special reference to lead, occupational cancer, early recognition and treatment of cancer of the stomach, sarcoma of bone, cancer cachexia, cancer of the lung, diagnostic methods in relation to cancer, the effects of radium and x-rays on the vascular systems, with special reference to malignant growth, and their biologic effects with reference to wave-length, etc., the geographic and racial prevalence of cancer, and public action in regard to cancer. The report is of interest to all who try to keep pace with the progress of the study of cancer.

**DEGENERATION AND REGENERATION OF THE NERVOUS SYSTEM** By S Ramon Y Cajal, M.D., F.R.S., Director of the Instituto Cajal, Madrid, Honorary Professor of Pathology in the University of Madrid. Translated and edited by Raoul M May, Ph.D. (Harvard), D.E.S. (Paris), Laboratoires d'anatomie et histologie comparees et de chimie biologique faculté des sciences, Paris. Two volumes Pp 769, with 317 illustrations London Oxford University Press, 1928

**LEHRBUCH DER ENTWICKLUNG DES MENSCHEN** Von Dr Alfred Fischel, O Professor der Embryologie und Vorstand des Embryologischen Institutes der Wiener Universität Price, 86 marks Pp 822, with 668 illustrations Berlin Julius Springer, 1929

**MANSON'S TROPICAL DISEASES** A Manual of the Diseases of Warm Climates Edited by Philip H Manson-Bahr, M.D., Physician to the Hospital for Tropical Diseases, London, etc. Ninth edition revised Price, \$11 Pp 921, with 476 illustrations New York William Wood and Company, 1929

## A STUDY OF CERTAIN EFFECTS OCCASIONED IN DOGS BY DIPHTHERIA TOXIN

### II ANALYSIS OF THE MECHANISM POSSIBLY RESPONSIBLE FOR THE ALTERATIONS OF THE HEART<sup>\*</sup>

HAROLD J STEWART, M D

NEW YORK

In a preceding paper<sup>1</sup> were reported certain results that followed the injection of diphtheria toxin into dogs. Among the results reported were changes in the size of the heart. An analysis of these changes in size forms the subject of this paper.

Following the intravenous injection into dogs of 0.00135 cc. or more of diphtheria toxin per kilogram of body weight, the animals became ill, lost weight, presented jaundice, showed urinary changes indicating irritation of the kidneys and died from two to nineteen days after the injection. There was, in most of these dogs, progressive decrease in the amplitude of the R<sub>2</sub> and R<sub>3</sub> waves of the electrocardiogram. The ratio of the weight of the left ventricle of the heart to that of the right ventricle (called hereafter the L/R ratio) was below the average for the hearts of normal dogs in all except one animal (no. 109). The ratio of the combined left and right ventricular weights to the body weight (called hereafter the  $\frac{L+R}{B.W.}$  ratio) in twelve dogs was below the normal average. In the remaining eight dogs it was equal to the normal average.

The method of injecting the diphtheria toxin into the dog was described in the first paper<sup>1</sup>. Briefly, diphtheria toxin having a minimal lethal dose for guinea-pigs of 0.00125 cc. was injected intravenously through the marginal ear veins. The toxin was diluted with sterile physiologic sodium chloride solution, and the dose was calculated in cubic centimeters per kilogram of body weight. Electrocardiograms and roentgenograms of the heart were made, and the body weight was taken immediately before the injection of the toxin. These observations were repeated

<sup>\*</sup> Submitted for publication, Nov. 12, 1928.

<sup>\*</sup> From the Hospital of the Rockefeller Institute for Medical Research.

1 Stewart, H. J. A Study of Certain Effects Occasioned in Dogs by Diphtheria Toxin. I. A Report of the Visceral Lesions, Arch. Path. to be published.

2 Levy, R. L. The Size of the Heart in Pneumonia. A Teleroentgenographic Study, with Observations on the Effect of Digitalis Therapy, Arch. Int. Med. **32**: 359 (Sept.) 1923.

3 Stewart, H. J. A Technique for Measuring X-Ray Photographs of the Cardiac Areas of Dogs. J. Clin. Investigation **3**: 475, 1927.

daily thereafter until the animals succumbed to the intoxication, or until further changes in those animals that survived were not observable. The roentgenograms of the heart were made at a distance of 2 meters, and the cardiac area was measured by the technic devised by Levy<sup>2</sup> and modified by Stewart<sup>3</sup> for use in dogs. The dogs were divided into two groups according to the amount of toxin injected per kilogram of body weight.

Four dogs (nos 81, 82, 83 and 84 of group 1, table 1) were given from 0.00161 to 0.00232 cc of diphtheria toxin per kilogram of body weight intravenously, and from one to four days later a second injection of from 0.00105 to 0.00168 cc per kilogram of body weight. These

TABLE 1—*The Effect of Diphtheria Toxin on the Cardiac Area and the Body Weight in Dogs of Group 1*

Dog	Time of Observation	Amount of Toxin Injected per Kg., Cc	Died	Weight		Area of Heart		Per Cent Change in	
				Kg	Per Cent of First Weight	Sq Cm	Per Cent of First Area	Weight	Area of Heart
81	Before injection			10.75	100.0	41.40	100.0		
	After injection								
	1 day	0.00232		9.80	91.2	29.63	71.3		
	2 days	0.00105	3d day	9.55	88.8	29.35	70.9	11.2	29.1
82	Before injection			12.45	100.0	53.03	100.0		
	After injection								
	1 day	0.00161		11.75	94.4				
	2 days			11.55	92.7	39.20	73.9		
	3 days			11.50	92.3	37.57	70.8		
	4 days	0.00166		10.85	87.1	37.50	70.7		
	5 days		5th day	10.20	81.9	30.63	57.7	18.1	42.3
83	Before injection			7.95	100.0	42.70	100.0		
	After injection								
	1 day	0.00166		8.00	100.6	34.50	80.7		
	2 days	0.00166		7.80	98.1	34.20	80.0		
	3 days		3d day	7.55	94.9	34.05	79.7	5.1	20.3
84	Before injection			8.90	100.0	38.40	100.0		
	After injection								
	1 day	0.00168		8.67	97.4	27.73	72.2		
	2 days	0.00168		8.37	94.1	27.55	71.7		
	3 days		3d day	7.85	88.2	22.75	59.2	11.8	40.8

dogs exhibited a remarkable decrease in the size of the heart shadow, ranging from 20 to 42 per cent (fig 1). The decrease was seen as early as twenty-four hours after the first injection. In dogs 81 and 83, it was at its maximum then, while in dogs 82 and 84 the area of the heart continued to decrease until the death of the animals, none of the animals surviving longer than five days after the first injection. This decrease in size is well seen in the roentgenograms of dog 82 (fig 2).

The question arose: To what mechanism was this decrease in size of the heart due? A number of possibilities presented themselves. The decrease might have been due (1) to the decrease in body weight that also took place or (2) to the toxin injected. If due to the latter, there should be a dose that would fail to cause this change. The toxin could



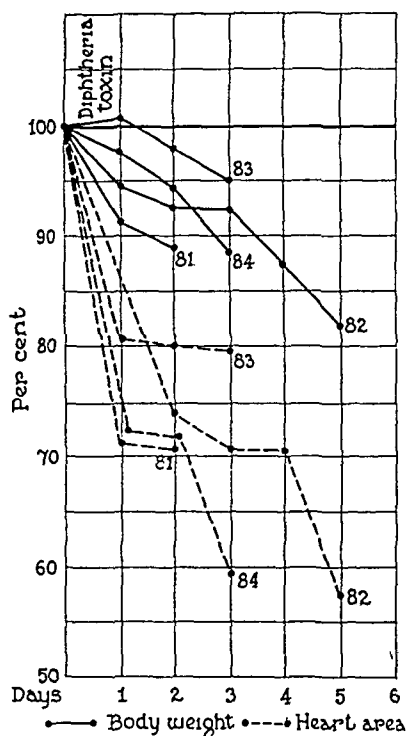


Fig 1—Graph showing the effect of diphtheria toxin on the cardiac area and the body weight in the dogs of group 1 (table 1) In this and in the succeeding figures, the lapse of days after the injection of the toxin is plotted on the abscissae The numbers at the ends of the curves refer to the dogs

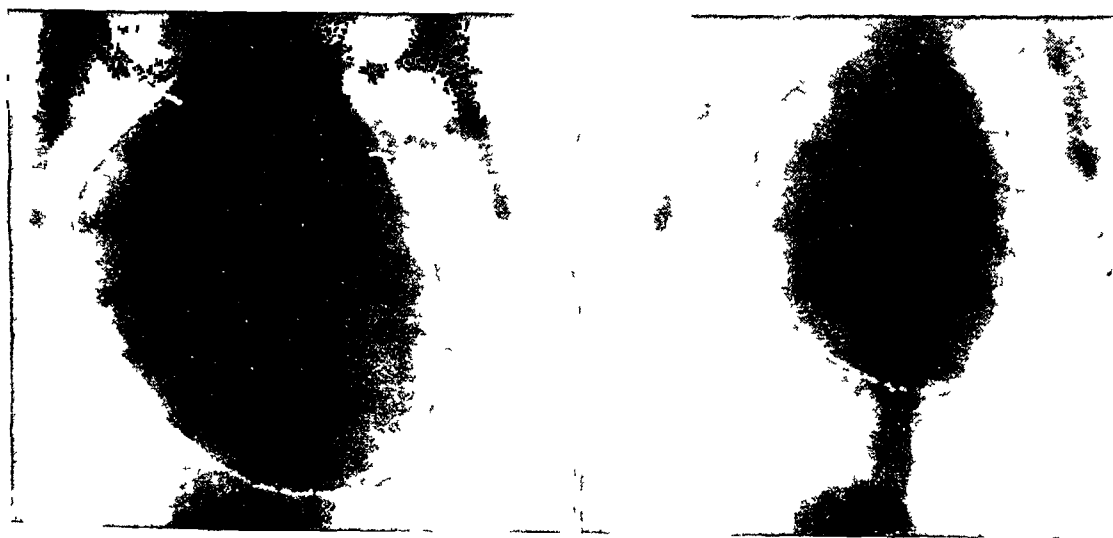


Fig 2—Roentgenogram of the heart of dog 82 *A* was taken Jan 4, 1923, before, and *B* was taken Jan 10, 1923, after a total of 0.00327 cc of diphtheria toxin per kilogram of body weight had been given

being about the decrease in several ways (1) by decreasing the total amount of the circulating blood, evidence of which might be found in a study of the number of red cells and the hemoglobin content of the blood, the blood volume and the microscopic sections of the organs after death, (2) by producing capillary dilatation, which would allow a redistribution of the blood in the body, (3) by destruction of the substance of the heart muscle, and (4) by an injury of the fibers of the heart muscle allowing a change in the water equilibrium, so that water would pass out of the cells and the cells be decreased in size. Each one of these possibilities was examined and the results are now reported.

## OBSERVATIONS

*Effect of a Decrease in Body Weight on the Area of the Heart—*

In the dogs of group 1 there was a loss in body weight of from 11 to 18 per cent, and a decrease in the size of the heart of from 20 to 42 per

TABLE 2—*The Effect of Fasting for Four Days on the Body Weight and the Cardiac Area in Normal Dogs*

Dog	Per Cent Change in Body Weight after Fasting Four Days	Per Cent Change in Area of Heart after Fasting Four Days
85 ♂	-12.0*	-7.6*
86 ♀	-7.7	+5.5
87 ♀	-6.5	-3.6
103 ♂	-10.3	-2.8
104 ♂	-9.0	+8.1
105 ♂	-14.4	+6.9
106 ♀	-10.7	-3.6

\* The negative sign indicates a decrease and the positive sign an increase.

cent (fig. 1). That the decrease in the area of the heart did not parallel and was not dependent on the loss in body weight is shown by the following experiments.

Seven dogs (nos. 85, 86, 87, 103, 104, 105 and 106) were not given food for from three to four days. They had water as desired. Roentgenograms were made before the period of fasting began and were repeated frequently throughout the period of fasting. The loss of body weight amounted to from 6 to 14 per cent (as recorded in table 2 and fig. 3A), while the cardiac area varied between a decrease of 7 per cent and an increase of 8 per cent (table 2, fig. 3B). These figures are within the limits of a variation of 10 per cent, which represents the error involved in the method. Although the fasting dogs showed approximately as great a decrease in body weight as did the dogs suffering from diphtheria intoxication, there was not a parallel decrease in the size of the heart. The loss in the dogs suffering from diphtheria intoxication, in all probability, was therefore due to the toxin and was not an aspect of the accompanying loss of body weight. The fasting dogs were later fed until they regained their former weight. They were then given diphtheria toxin. Promptly they showed a decrease in the size of the heart (fig. 2). Further evidence exhibiting the absence of parallelism between the loss of body weight and the decrease of cardiac area was furnished by the dogs in group 2C (nos. 88, 89, 90 and 101 of table 3 and fig. 4). They received

only 0.001 cc per kilogram of body weight, which was a dose too small to produce death. They showed as great a loss of weight as the dogs given the larger dose, yet a decrease in cardiac area did not accompany this loss in weight. In addition, dog 108 (table 4, fig 5) which received 0.00135 cc of toxin per kilogram of body weight did not show changes in body weight, but did show a decrease in the size of the heart.

*Effect of Diphtheria Toxin on the Area of the Heart*—Since the dogs of group 1 that received a total of from 0.00327 to 0.00337 cc of diphtheria toxin per kilogram of body weight showed striking decreases in cardiac area, it was important to learn how much toxin was necessary to bring about this condition. To acquire data on this point, I gave

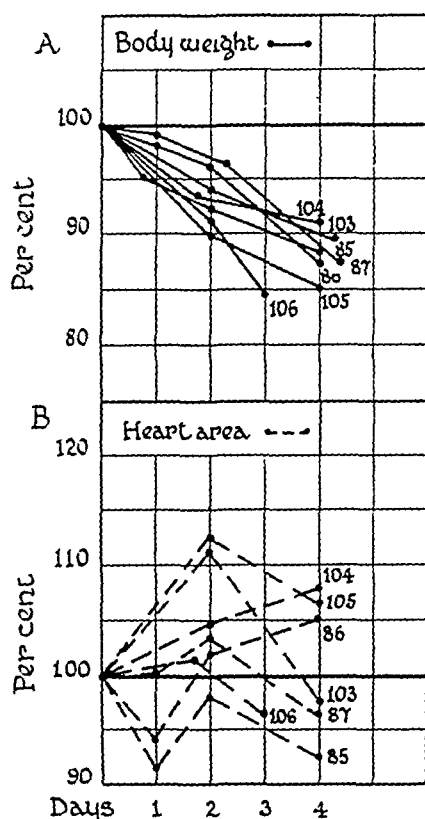


Fig 3—Graph A shows the effect of fasting on the body weight of dogs, graph B, the effect on the cardiac area

decreasing dose of toxin to a second group of dogs, group 2 A being given 0.00168 cc, group 2 B, 0.00135 cc and group 2 C, 0.001 cc per kilogram of body weight

In group 2 A, in which nine dogs (nos 85, 86, 87, 97, 99, 102, 103, 104 and 105 of table 5) received, in a single injection, 0.00168 cc per kilogram of diphtheria toxin, decrease in the area of the hearts promptly took place to the extent of from 19 to 39 per cent. The decrease in body weight was from 4 to 17 per cent (fig 6). The animals died from two and a half to five days after the first injection. These changes were as great as those observed in the dogs receiving two injections (group 1).

TABLE 3—*The Effect of Diphtheria Toxin on the Cardiac Area and the Body Weight in Dogs of Group 2 C*

Dog	Time of Observation	Amount of Toxin Injected per Kg, Cc	Died	Weight		Cardiac Area	
				Kg	Per Cent of First Weight	Sq Cm	Per Cent of First Area
88 ♂	Before injection	0.001		7.92	100.0	25.70	100.0
	After injection						
	1 day			7.46	94.1	27.35	106.4
	2 days			7.20	90.9	26.78	104.2
	3 days			7.20	90.9	27.75	107.9
	4 days			7.05	89.0	26.40	102.7
	6 days			7.20	90.9	23.18	109.7
	7 days			6.85	86.4	26.65	103.7
	9 days			6.80	85.8	27.95	108.7
	11 days			6.65	83.9	25.20	98.0
	14 days		Lived	6.80	90.9	27.30	106.2
89 ♀	Before injection	0.001		6.70	100.0	27.35	100.0
	After injection						
	1 day			6.43	95.9	26.18	95.7
	2 days			6.40	95.5	26.50	96.9
	3 days			6.50	97.0	26.40	96.5
	4 days			6.35	94.7	28.68	104.8
	6 days			6.15	91.7	27.80	101.6
	7 days			5.85	87.3	26.85	98.1
	9 days			5.90	88.0	25.35	92.6
	11 days			5.75	85.8	28.60	104.5
	14 days		Lived	6.10	91.0	25.65	93.7
90 ♂	Before injection	0.001		11.20	100.0	39.55	100.0
	After injection						
	1 day			11.15	99.5	37.30	94.5
	2 days			11.05	98.6	39.70	100.3
	3 days			10.95	97.7	41.30	104.4
	4 days			10.70	95.5	40.45	102.2
	6 days			10.20	91.0	37.60	95.0
	7 days			10.05	89.7	37.15	93.9
	9 days			9.70	86.6	36.75	92.9
	11 days			9.95	88.8	41.30	104.4
	14 days		Lived	10.20	91.0	38.35	96.9
101 ♀	Before injection	0.001		12.30	100.0	39.40	100.0
	After injection						
	1 day			12.00	97.5	39.80	101.0
	2 days			11.90	96.7	37.60	95.4
	3 days			12.25	99.6	43.45	109.7
	4 days			11.65	94.7	42.80	108.6
	5 days			11.90	96.7	45.55	118.1
	7 days			11.15	90.6	43.65	110.7
	10 days			10.43	84.7	38.20	96.9
	15 days		Lived	11.82	96.1	39.10	99.2
106 ♀	Before injection	0.001		11.57	100.0	39.35	100.0
	After injection						
	1 day			11.50	99.4	38.30	97.3
	2 days			11.30	97.6	36.75	93.4
	3 days			10.81	93.4	34.75	88.3
	4 days			11.11	96.0	32.40	82.3
	6 days			10.39	89.8	34.75	88.3
	7 days			9.93	86.2	35.40	89.9
	8 days			9.67	83.5	31.80	80.8
	9 days			9.40	81.2	33.40	84.8
	14 days			7.10	61.3	33.70	85.6
	20 days			7.50	64.8	41.75	106.0
	23 days		23d day	7.05	60.9	37.75	94.9

TABLE 4—*The Effect of Diphtheria Toxin on the Cardiac Area and the Body Weight in the Dogs of Group 2B*

Dog	Time of Observation	Amount of Toxin Injected per Kg, Cc	Died	Weight		Cardiac Area		Per Cent Change in	
				Kg	Per Cent of First Weight	Sq Cm	Per Cent of First Area	Weight	Cardiac Area
107 ♂	Before injection	0.00135		17.18	100.0	66.50	100.0		
	After injection								
	1 day			17.41	101.3	51.10	76.8		
	2 days			15.80	91.9	50.45	75.8		
	3 days			15.83	92.1	56.45	84.8		
	5 days			15.96	92.3	55.85	83.9		
	6 days			16.00	93.1	51.10	76.8		
	8 days			15.30	89.0	50.70	76.3		
	9 days			14.90	86.7	47.70	71.7		
	10 days			14.51	84.4	42.80	64.3		
	12 days			14.10	82.0	40.25	60.5		
	13 days			13.90	80.9	43.30	65.1		
	14 days			13.85	80.6	42.65	64.1	19.4	35.9
	15 days		16th day	13.50	78.5	*			
108 ♂	Before injection	0.00135		19.15	100.0	57.80	100.0		
	After injection								
	1 day			19.22	100.3	59.70	103.2		
	2 days			19.55	102.0	55.60	96.1		
	3 days			19.40	101.3	48.60	84.0	+1.3	16.0
	4 days		4th day						
109 ♂	Before injection	0.00135		15.38	100.0	51.85	100.0		
	After injection								
	1 day			15.25	99.1	49.90	96.2		
	2 days			15.35	99.8	43.80	84.4		
	3 days			14.93	97.0	45.55	87.8		
	5 days			14.24	92.5	41.80	80.6		
	6 days			14.65	95.2	47.60	91.8		
	8 days			14.30	92.9	49.45	95.3		
	9 days			13.85	90.1	51.60	99.5		
	10 days			13.50	87.7	47.70	91.9		
	12 days			13.27	86.3	45.55	87.8		
	13 days			12.90	83.8	43.00	82.9		
	14 days			12.85	83.5	38.50	74.2		
	15 days			12.55	81.6	46.70	90.2		
	16 days			12.40	80.6	42.20	81.3		
	17 days		18th day	12.03	78.2	43.20	83.3	21.8	16.7
110 ♂	Before injection	0.00135		13.85	100.0	48.80	100.0		
	After injection								
	1 day			14.15	102.1	41.35	84.7		
	2 days			13.88	100.2	42.25	86.5		
	3 days			13.45	97.1	45.30	92.8		
	5 days			12.90	93.1	43.65	89.3		
	6 days			12.85	92.7	41.25	84.5		
	8 days			12.10	87.4	42.40	86.8		
	9 days			11.80	85.1	43.70	89.5		
	10 days			11.40	82.3	32.90	67.4		
	11 days			10.97	79.9	33.15	67.9		
	13 days			10.85	78.3	31.00	63.5	21.7	36.5
	14 days			10.75	77.6	32.90	67.4		
	15 days			10.53	76.0	33.45	68.5		
	16 days			10.38	74.9	35.55	72.8		
	17 days			10.25	74.0	34.15	69.9	26.0	30.1
	19 days			9.96	71.8	*			
	20 days		20th day	9.65	69.6	*			
111 ♂	Before injection	0.00135		16.45	100.0	49.70	100.0		
	After injection								
	1 day			16.08	97.7	44.50	89.5		
	2 days			15.85	96.3	41.85	84.3		
	3 days			15.70	95.2	42.20	84.9		
	5 days			15.55	94.5	43.35	87.2		
	6 days			15.18	91.6	37.90	76.3	8.4	23.7
	8 days			14.80	89.9	41.80	84.1		
	9 days			14.05	85.4	40.50	81.0		
	10 days		11th day	13.64	82.9	41.90	84.3	17.1	15.7

\* The heart shadow was not distinct enough to be outlined

TABLE 4—*The Effect of Diphtheria Toxin on the Cardiac Area and the Body Weight in the Dogs of Group 2 B—Continued*

Dog	Time of Observation	Amount of Toxin Injected per Kg., Cc.	Died	Weight		Cardiac Area		Per Cent Change in	
				Kg	Per Cent of First Weight	Sq Cm	Per Cent of First Area	Weight	Cardiac Area
112 ♂	Before injection	0.00135		14.70	100.0	37.95	100.0		
	After injection								
	1 day			15.00	102.0	50.15	83.5		
	2 days			15.12	102.8	50.85	87.7		
	3 days			14.88	101.2	57.90	99.9		
	5 days			15.15	103.0	53.60	92.4		
	6 days			14.62	99.4	49.40	85.2		
	8 days			14.20	95.5	50.70	87.4		
	9 days			13.65	92.8	50.38	86.7		
	10 days			13.02	88.5	43.80	75.5		
	12 days		13th day	12.55	85.3	43.90	75.7	14.7	24.3

In group 2 B, in which six dogs (nos 107, 108, 109, 110, 111 and 112 of table 4) received 0.00135 cc per kilogram of toxin, dog 108 became acutely ill and died on the fourth day after the injection, the other five dogs gradually became ill and died from twelve to nineteen days after the injection. The decrease in cardiac area was, on the average, as great as in those receiving the larger doses. In four dogs (nos 107, 110, 111 and 112 of fig 5B) the decrease was shown on the day following the injection, and in two dogs (nos 108 and 109) a definite decrease in cardiac size did not take place until the second or third days after the injection. The size of the heart did not decrease as steadily as in the dogs receiving 0.00168 cc per kilogram of body weight, the decrease was more gradual and fluctuated (as in dog 109). The loss of body weight observed in these dogs was greater than that observed in the other groups, presumably because the animals survived for a longer time (fig 5A).

In group 2C, in which five dogs (nos 88, 89, 90, 101 and 106 of table 3) received 0.001 cc of toxin per kilogram of body weight, the clinical course of dog 106, which survived the injection only twenty-three days, was somewhat similar to that of the animals in group 2B, the other four dogs did not show decreases in cardiac size (fig 4B), although they lost as much weight immediately following the toxin injections as did the dogs given the larger dosages (fig 4A). These dogs were living and well twelve months after receiving the toxin.

**Summary** From these experiments, it is clear that the decrease in the size of the heart was dependent on the diphtheria toxin. Doses of 0.00135 cc or more per kilogram of body weight resulted in decreases in the area of the heart, while doses of 0.001 cc per kilogram of body weight were without effect.

*Effect of Diphtheria Toxin on the Amount of the Circulating Blood*—I next studied the animals with a view to learning whether a decrease in the amount of the circulating blood took place. These studies were made in dogs into which had been injected 0.001 and 0.00168 cc of toxin per kilogram of body weight.

**Method** To ascertain whether blood destruction occurred after the injection of the diphtheria toxin, I counted the red blood cells and made estimations of the hemoglobin (expressed as oxygen capacities). As these do not give any indication of the volume of whole blood in circulation, estimations of blood volume were

also carried out. The red cells were counted in blood obtained from the ear by a needle. The blood used for the estimations of oxygen capacity was taken from that drawn from a femoral artery in the course of the measurements of the blood volume. The analyses for oxygen capacity were made according to a method described by van Slyke and Neill,<sup>4</sup> the van Slyke manometric apparatus being used. The estimations of the blood volume were made by the vital red method introduced by Keith, Rowntree and Geraghty.<sup>5</sup>

Vital red was used in 15 per cent solution in freshly distilled water. Of this solution, 1 cc was injected for each 5 Kg of body weight. The standard

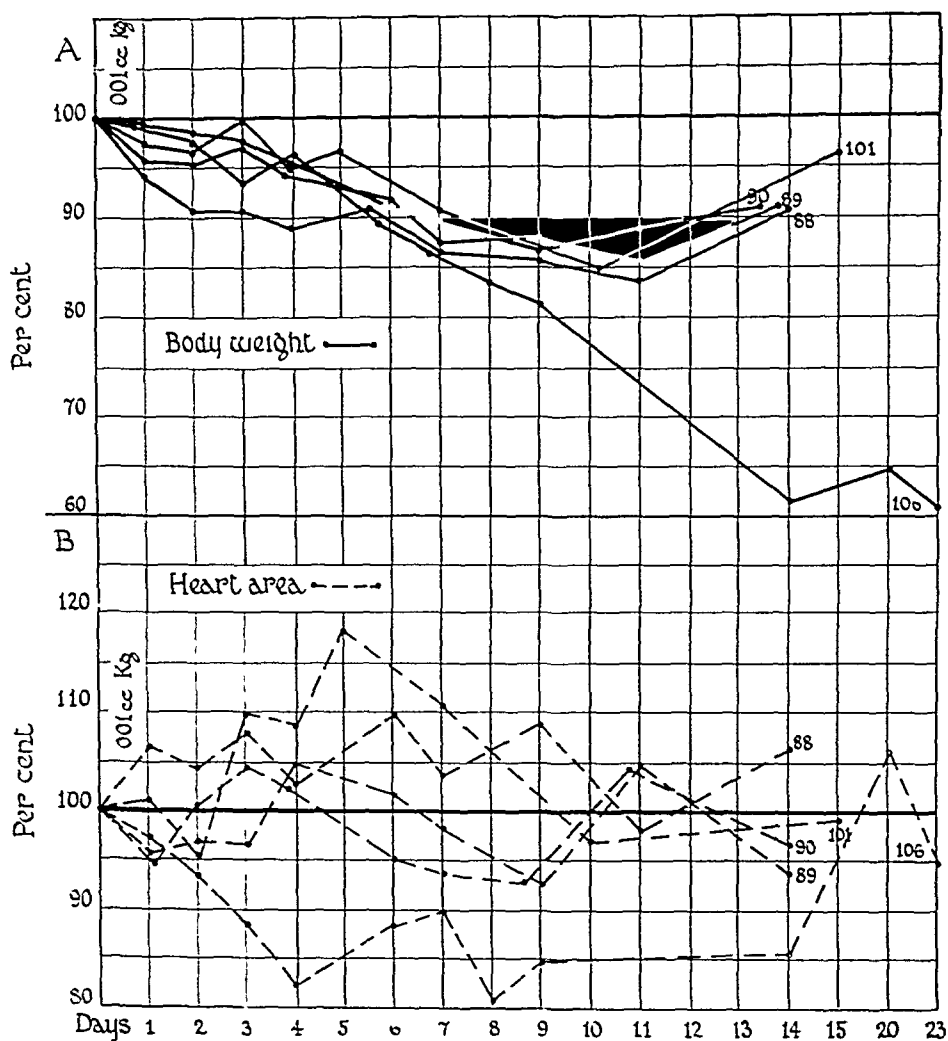


Fig 4—Graph A shows the effect of diphtheria toxin on the body weight and graph B the effect on the cardiac area in the dogs of group 2 C (table 3)

was made of one part of dye diluted 1:200, one part control plasma (that is plasma of the blood taken before the injection of the dye) and two parts of 0.9 per cent sodium chloride. The blood used as control was drawn from a femoral

<sup>4</sup> Van Slyke, D. D., and Neill, J. M. The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement. *J. Biol. Chem.* **61**: 523, 1924.

<sup>5</sup> Keith, N. M., Rowntree, L. G., and Geraghty, J. T. A Method for the Determination of Plasma and Blood Volume. *Arch. Int. Med.* **16**: 547 (Oct.) 1915.

TABLE 5—*The Effect of Diphtheria Toxin on the Cardiac Area and the Body Weight in the Dogs of Group 2 A*

Dog	Time of Observation	Amount of Toxin Injected per Kg Cc	Died	Weight		Cardiac Area		Per Cent Change in	
				Kg	Per Cent of First Weight	Sq Cm	Per Cent of First Area	Weight	Cardiac Area
85 ♂	Before injection	0.00168*		7.00	100.0	27.70	100.0		
	After injection								
	1 day			6.30	90.0	28.50	102.8		
	2 days			6.30	90.0	24.25	87.5		
	3 days			6.05	86.4	23.63	85.3		
	5 days			5.80	82.8	19.55	70.5	17.2	29.5
	6 days			5.62	80.3	20.20	72.8		
	7 days			5.62	80.3	25.80	93.1		
	8 days		8th day	5.50	78.5	27.50	99.2	21.5	0.8
86 ♀	Before injection	0.00168		9.77	100.0	35.40	100.0		
	After injection								
	1 day			9.00	93.1	29.70	83.8		
	2 days			8.80	90.0	24.40	68.9	10.0	31.1
	3 days		3d day	8.55	87.5	25.65	72.4	12.5	27.6
87 ♀	Before injection	0.00168		16.10	100.0	51.75	100.0		
	After injection								
	1 day			15.15	94.0	45.40	87.7		
	2 days			14.45	89.7	33.50	64.7		
	3 days		3d day	13.90	86.3	33.35	64.4	13.7	35.6
97 ♀	Before injection	0.00168		16.20	100.0	51.65	100.0		
	After injection								
	1 day			16.00	98.7	43.15	83.5		
	2 days			15.60	96.3	38.50	74.5		
	3 days		3d day	15.50	95.7	34.70	67.2	4.3	32.8
99 ♂	Before injection	0.00168		14.00	100.0	57.15	100.0		
	After injection								
	1 day			13.40	95.7	50.48	88.3		
	2 days			13.25	94.6	43.80	76.6		
	3 days			13.30	95.0	39.75	69.5	5.0	30.5
	4 days			13.20	94.3	42.05	73.5		
	5 days		5th day	13.20	94.3	40.60	71.0	5.7	29.0
102 ♂	Before injection	0.00168		14.00	100.0	52.35	100.0		
	After injection								
	1 day			13.70	97.9	32.75	62.5		
	2 days			13.50	96.4	39.60	75.6		
	3 days			13.10	93.6	34.80	66.4		
	4 days		4th day	12.30	87.9	31.70	60.5	12.1	39.5
103 ♂	Before injection	0.00168		11.20	100.0	38.45	100.0		
	After injection								
	1 day			10.85	96.8	31.50	81.9		
	2 days			10.95	97.7	32.70	80.4		
	3 days			10.75	95.9	35.60	92.5		
	4 days		4th day	10.32	92.1	25.75	66.9	7.9	33.1
104 ♂	Before injection	0.00168		9.02	100.0	36.40	100.0		
	After injection								
	1 day			8.76	97.1	34.10	93.5		
105 ♂	2 days		2d day	8.70	95.7	28.40	77.9	4.3	22.1
	Before injection	0.00168		11.12	100.0	43.85	100.0		
	After injection								
	1 day			10.80	97.1	36.10	82.3		
	2 days			11.40	102.5	37.35	85.1		
	3 days			10.95	98.4	38.10	86.8		
	4 days			10.92	98.2	34.00	77.5	1.8	20.5
	5 days		5th day	10.60	95.3	35.70	81.4	4.7	18.6

\* The dog moved during the injection so that about one half was given subcutaneously



artery, the dye was then injected into a superficial vein of that same leg, in from four to five minutes, the second sample of blood was drawn from the opposite femoral artery. The femoral artery was used for obtaining the sample because it is superficial in dogs, it is easily punctured with a needle and as large a sample may be obtained as is necessary. Stasis is thereby avoided. Pressure was applied for a few minutes over the artery after the removal of the needle to prevent extravasation of blood into the tissues. Potassium oxalate was used as an anticoagulant. Hematocrit readings were made after three Epstein tubes had been filled, one with each specimen of blood, and centrifuged until further centrifugation did not give any change in the packing of the cells.

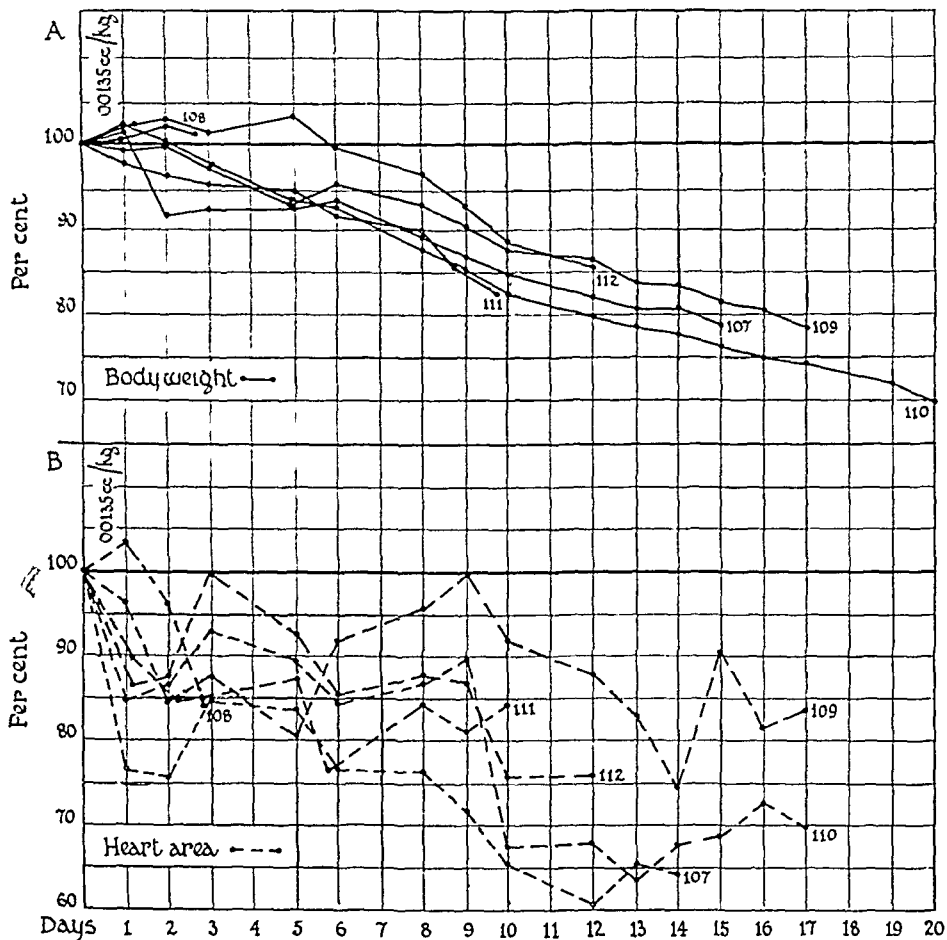


Fig 5—Graph A shows the effect of diphtheria toxin on the body weight, and graph B that on the cardiac area in the dogs of group 2 B (table 4)

Effect of Diphtheria Toxin on the Number of Red Cells and Hemoglobin. Five animals in group 2A that exhibited decrease in size of the heart did not show any change in the red blood cell count following the injection of 0.00168 cc of diphtheria toxin per kilogram of body weight (dogs 97, 99, 102, 103 and 105 of table 6 and fig 7). One of the dogs (no 97) did not show any change in the oxygen capacity of the blood, the other four showed a slight increase. Of the two animals that received 0.001 cc per kilogram of body weight, a dose that was without effect on the size of the heart, one (dog 101) showed a 33 per cent decrease in the red blood cell count with a smaller decrease of 6 per cent

in the oxygen capacity. The other animal (dog 106) did not show any change in the red blood cell count and the capacity for oxygen. Dogs 99, 102 and 103, which were given 0.00168 cc toxin per kilogram of body weight exhibited an increase in the proportion of cells to plasma, according to the hematocrit readings, dogs 97 and 105, which received the same amount of toxin per kilogram of body weight, and dogs 101 and 106, which received 0.001 cc per kilogram, did not show any deviation in the hematocrit readings. The hematocrit readings agree with the estimations of capacity for oxygen because they were made from arterial blood, in those instances in which there is a divergence of the red cell counts from the figures that one would expect from the oxygen capacity and the hematocrit readings, it is likely that the discrepancy is due to the fact that the blood for the red blood cell counts was taken from the superficial vessels of the ear, where the concentration of cells was possibly different from the concentration in the arterial blood.

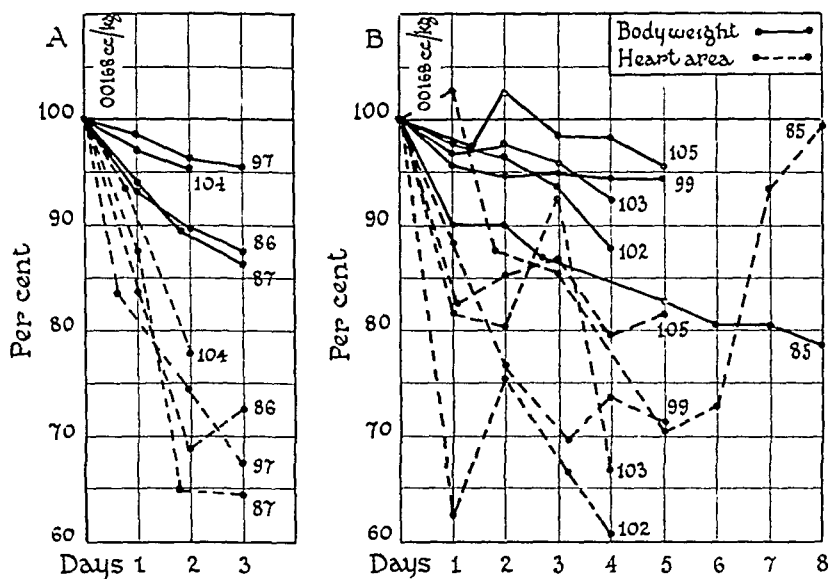


Fig 6—Graph A shows the effect of diphtheria toxin on the cardiac area, and graph B the effect on the body weight in the dogs of group 2A (table 5)

**Summary** There was, then, no decrease in the number of red blood cells, in the amount of hemoglobin, or in the relative proportion of cells to plasma in five dogs in which there was a decrease in cardiac area. One of two dogs that received a dose of toxin too small to affect the area of the heart, showed a slight decrease in the number of red blood cells and in the amount of hemoglobin while the other dog did not show any change. These data indicate that destruction of red blood cells was not a factor in the mechanism responsible for the decrease in the cardiac area.

**Effect of Diphtheria Toxin on the Blood Volume** Estimations of blood volume were made on five dogs before and after injections of diphtheria toxin. The total blood volume of dog 101 (table 6, fig 7) was 1,282 cc before the injection of toxin, three days after the injection of toxin, it was 1,041 cc. This dog, which had been given 0.001 cc per kilogram of body weight and which showed a decrease of 18 per cent in blood volume, did not present any significant change in the size of the heart. Before the injection of toxin into dog 102, the blood

volume was 1,864 cc. It was 1,739 cc three days after the injection, a decrease of 6 per cent (this is within the limits of error of the method) at a time when the cardiac area was decreased 33 per cent. The estimations for dog 103 revealed an increase in the total blood volume of 26 per cent on the third day after the injection of toxin, while the cardiac area showed a decrease of 19 per cent. There was an increase of 6 per cent in the blood volume of dog 105, while the area of the heart was decreased 13 per cent from that before the injection. Dog 106 showed a decrease of 12 per cent in the total blood volume accompanying a decrease of 11 per cent in the area of the heart.

TABLE 6—*The Effect of Diphtheria Toxin on the Blood Volume, the Number of Red Blood Cells, the Hemoglobin and the Size of the Heart in Dogs*

Dog	Time of Observation	Hemato- crit Reading, per Cent Cells	Red Cell Count, Millions	Hemoglobin of Oxygen Capacity per Cent by Volume	Plasma, Cc	Whole Blood, Cc	Cardiac Area, Sq Cm	Amount of Toxin Injected per Kg, Cc
97	Before injection	41.6	8.9	21.52			51.65	
	Third day after	43.5	9.2	21.66			34.70	0.00168
	Percentage change*	+1.9	+3.3	+0.6			-32.8	
99	Before injection	43.8	8.7	23.59			57.15	
	Third day after	55.5	8.5	28.62			39.75	0.00168
	Percentage change	+11.7	-2.3	+21.2			-30.5	
102	Before injection	39.2	10.1	21.06	1,136	1,864	52.35	
	Third day after	50.9	9.7	22.96	854	1,739	34.80	0.00168
	Percentage change	+11.7	-4.0	+9.4	-24.9	-6.7	-33.6	
103	Before injection	43.3	8.3	20.98	608	1,074	38.45	
	Second day after	51.5	8.3	24.40	658	1,357	32.70	0.00168
	Percentage change	+8.2	0.0	+16.3	+8.2	+26.3	-19.6	
104	Before injection	41.4	7.7	21.72	657	1,121	36.45	
	Second day after						28.40	0.00168
	Percentage change						-22.1	
105	Before injection	37.3	6.8	17.01	793	1,265	43.85	
	Third day after	39.0	7.0	18.40	823	1,349	38.10	0.00168
	Percentage change	+1.7	+2.9	+8.1	+3.7	+6.6	-13.2	
106	Before injection	48.3	8.5	22.78	1,032	1,996	39.35	
	Third day after	49.7	8.7	22.16	871	1,731	34.75	0.001
	Percentage change	+1.4	+2.3	-2.7	-15.6	-12.8	-11.7	
101	Before injection	24.9	7.1	10.18	964	1,282	39.40	
	Third day after	23.6	4.7	9.57	795	1,041	43.45	0.001
	Percentage change	-1.3	-33.8	-6.0	-17.6	-18.8	+9.7	

\* The positive sign indicates an increase, the negative sign a decrease.

**Summary** Following the injection of diphtheria toxin, one dog showed a decrease of blood volume and not any change in the size of the heart, two did not show any change in blood volume and did show decreases in the cardiac area, one showed an increase in blood volume and a decrease in cardiac area, and one, a slight decrease in blood volume accompanying a slight decrease in cardiac area (table 7).

Of the four dogs showing a decrease in cardiac area, only one showed a decrease in total blood volume. From these few experiments, the limits of error of the method of estimating blood volume being taken into consideration, the volume does not appear to have changed and therefore could not have been a factor in bringing about the decrease in cardiac size.

**Effect of a Change in the Blood Volume on the Area of the Heart** On account of the lack of relationship between the cardiac size and the blood volume

in these experiments, it seemed important to learn precisely what the effect on the size of the heart is when the blood volume is altered. The following experiment was devised to show the effect of a change in blood volume on the size of the heart. A known amount of blood was taken from a dog, and the effect on the size of the heart was observed. The blood withdrawn from this dog (no 1) was transfused into another dog (no 2), and the effect of the increase in blood volume was observed. Dog 116, weighing 13.44 Kg, presumably had a total blood volume of approximately 1,200 cc. After a roentgenogram of the heart had been taken, 500 cc of blood was removed from the left femoral artery. The dog was in place on the roentgen-ray table during this procedure. Roentgenograms were made immediately after the blood had been withdrawn, at short intervals during that day, and then daily. Counts of the red blood cells were made at the same time that the roentgenograms were made. There was a sharp fall of 20 per cent (table 8, fig 8A) in the cardiac area immediately after the

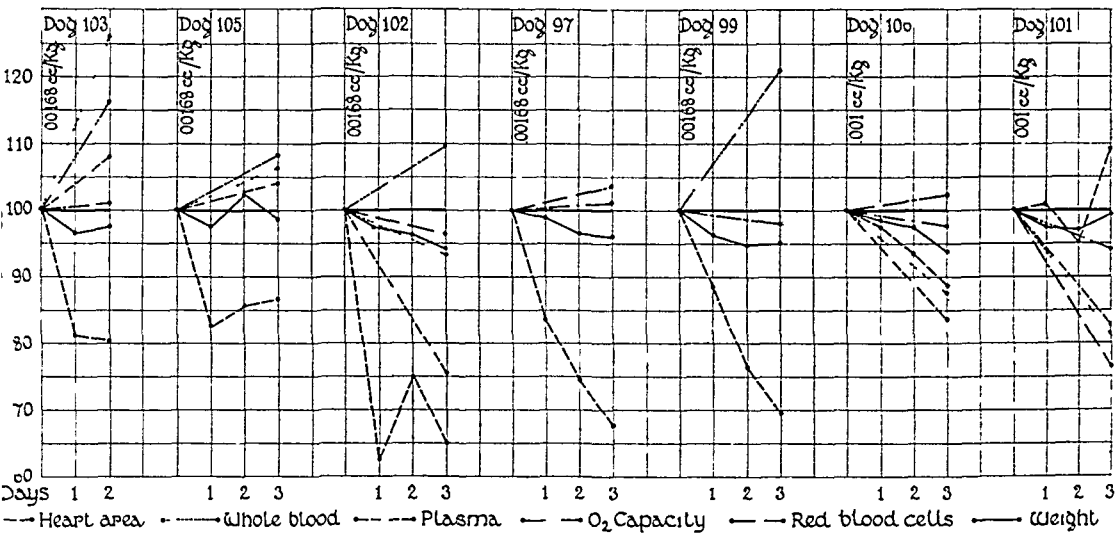


Fig 7—A graph showing the effect of diphtheria toxin on the hemoglobin the number of red blood cells and blood volume in dogs (table 6). The cardiac areas and the body weights of the corresponding dogs are also plotted.

blood had been removed, and this fell further to 25 per cent in two hours and forty minutes. The count of the red blood cells did not show any change until the day after the bleeding, then the count was found to have decreased 17 per cent and the following day 30 per cent, probably owing to the dilution of the blood in the body's attempt to restore the blood volume to normal. The cardiac area showed a decrease of from 20 to 30 per cent for six days; it then returned to 88 per cent of the area first observed, and remained at this figure for one month. At the time of the return of the cardiac area to 88 per cent of its initial size, the count of the red blood cells had still further decreased, indicating a further dilution of the blood.

The 500 cc of blood removed from dog 116 was collected under sterile procedure. Clotting was prevented by the addition of 3 per cent sodium citrate to a final dilution of 0.3 per cent. This blood was transfused into dog 115, weighing 11.96 Kg. The blood of dog 115 had beforehand been cross-agglutinated

against the blood of dog 116 by the rapid method of Rous and Turner.<sup>6</sup> Dog 115 presumably had a blood volume of approximately 1,000 cc, by the addition of 500 cc of blood, the total blood volume was increased about 50 per cent. Roentgenograms and counts of the red blood cells were made immediately after the transfusion and at short intervals later. Immediately after the transfusion was completed, the cardiac area increased 8 per cent (table 9, fig 8B). The next day it was only 2 per cent greater than it had been in the beginning. Since the position of the dog was not changed between the taking of the first roentgenogram and that immediately after the transfusion, this 8 per cent increase in size is significant. Three days after the transfusion, the area had decreased to

TABLE 7—Summary of the Changes in Blood Volume with the Corresponding Changes in Cardiac Area in Dogs Following the Injection of Diphtheria Toxin

Dog	Cardiac Area	Blood Volume
101	No change	Decrease
102	Decrease	No change
103	Decrease	Increase
105	Decrease	No change
106	Decrease	Decrease

TABLE 8—The Effect of Decreasing the Blood Volume by 500 Cc on the Cardiac Area and the Number of Red Blood Cells (Dog 116)

Time of Observation	Weight		Cardiac Area		Red Cells	
	Kg	Per Cent of First Weight	Sq Cm	Per Cent of First Area	Millions	Per Cent of First Count
Before bleeding	13.44	100.0	47.80	100.0	7.2	100.0
Immediately after bleeding			38.60	80.7		
Hours after bleeding						
1.6			36.20	75.7	6.8	94.4
2.6			35.45	74.1	7.0	97.2
6.1			42.35	88.5	6.9	95.9
21	12.27	91.3	37.20	77.8	7.0	97.2
27			39.60	82.8	6.0	83.3
Days after						
2	12.62	89.4	37.45	78.3	5.1	70.8
3	12.40	93.0	34.00	71.1	5.7	79.1
5	12.75	94.8	39.10	81.5	5.6	77.7
6	12.15	90.4	36.70	76.6	5.5	76.3
7	12.75	94.8	39.60	82.8		
8	12.25	91.1	42.20	88.2	4.2	58.3

91 per cent of its original size, and on the fifth day to 83 per cent. The cause of the secondary decrease is not clear. The count of the red blood cells increased 25 per cent immediately after the transfusion and, with slight fluctuations, continued to rise until the eighth day, when the increase reached 42 per cent. The amount of the urine of this dog was large during the first two days after the transfusion.

**Summary.** It may be seen, then, that a decrease in blood volume decreased the size of the heart, and a corresponding increase in blood volume increased the size of the heart slightly. That the increase in the latter case was not as great as one might have expected was probably due to the elasticity and distensibility of the vascular bed which can take care of the increased blood volume without great dilatation of the heart.

<sup>6</sup> Rous, P., and Turner, J. R. A Rapid and Simple Method of Testing Donors for Transfusion, J. A. M. A. 64: 1980 (June 12) 1915.

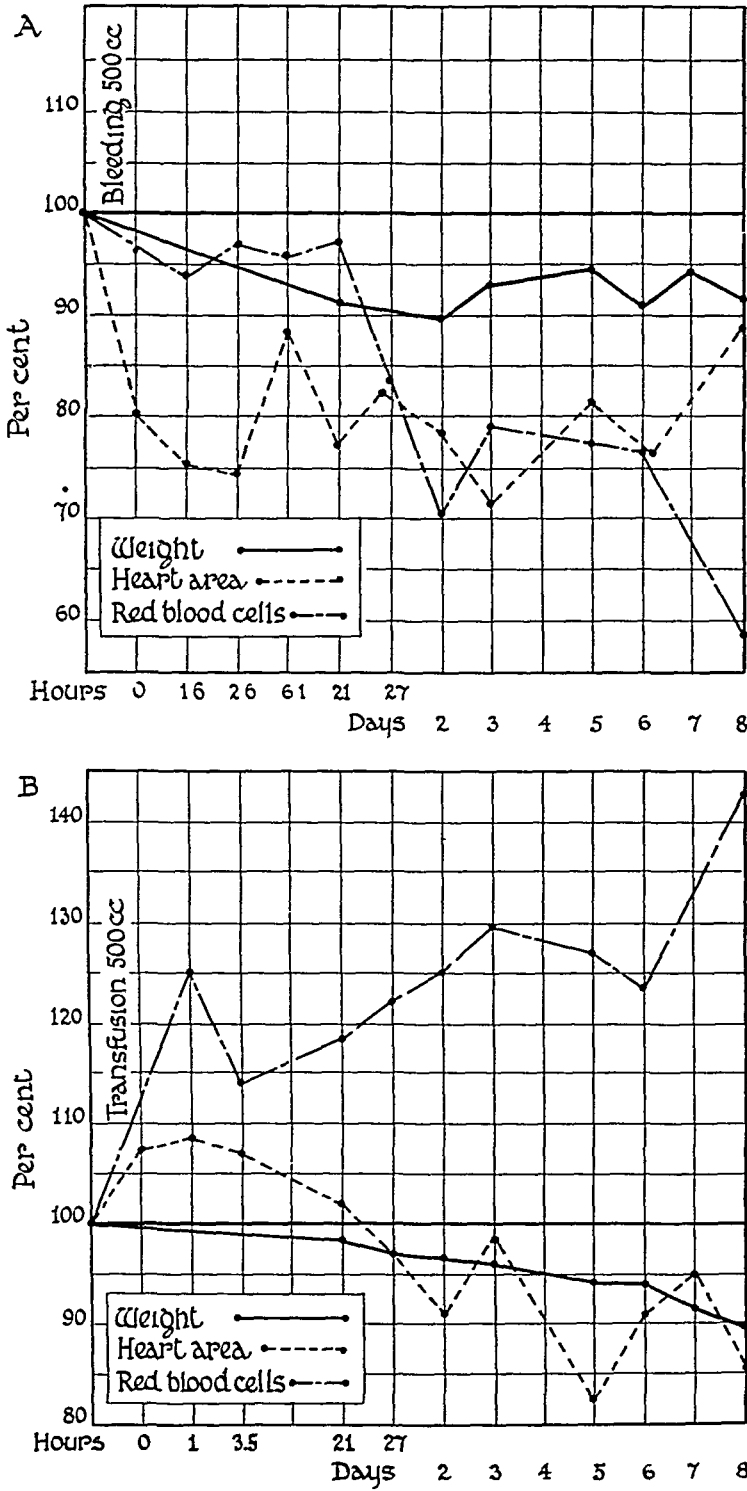


Fig 8—Graph *A* shows the effect of a decrease in blood volume on the cardiac area and the number of the red blood cells, graph *B* the effect of an increase in the volume of the blood

Effect of Diphtheria Toxin on the Regeneration of Red Blood Cells Although counts of the red blood cells and studies of the blood volume do not point to destruction of blood as the cause of the decrease in cardiac size, jaundice seen in many of the dogs suggested that it might have occurred. In sections from some of the livers there were nests of cells<sup>1</sup> suggestive of foci of regenerating red blood cells, and, in some of these, cells resembling nucleated red blood cells were seen. It is unusual that signs of regeneration of red blood cells should appear so early after the injury, and, in addition, the liver is not commonly supposed to take on the function of formation of red blood cells until considerable anemia is present, or until damage has been suffered by the other blood-forming organs. The sections of the liver occasionally showed bile thrombi, but they were not present in the livers of all the animals exhibiting jaundice, therefore, this could not be the factor that caused jaundice. It is possible that jaundice was caused by destruction of red blood cells by the toxin, indeed, the destruction of a small amount of blood might readily have given rise to sufficient pigment

TABLE 9—*The Effect of Increasing the Blood Volume by 500 Cc on the Cardiac Area and the Number of Red Blood Cells (Dog 115)*

Time of Observation	Weight		Cardiac Area		Red Cells	
	Kg	Per Cent of First Weight	Sq Cm	Per Cent of First Area	Millions	Per Cent of First Count
Before transfusion	11.96	100.0	47.55	100.0	6.4	100.0
Immediately after transfusion			51.35	107.9		
Hours after						
1			51.50	108.3	8.0	125.0
3.5			51.00	107.2	7.3	114.0
21	11.75	98.2	48.53	102.0	7.5	118.7
27			46.30	97.3	7.8	121.8
Days after						
2	11.55	96.5	43.45	91.3	8.0	125.0
3	11.45	95.7	46.68	98.1	8.3	129.6
5	11.25	94.0	39.35	82.7	8.1	126.5
6	11.25	94.0	43.30	91.0	7.9	123.4
7	10.95	91.5	45.25	95.1		
8	10.75	89.8	40.60	85.4	9.1	142.5

to cause jaundice, although the decrease in the total number of red blood cells and the total blood volume was too small to be detected by the methods used.

Summary. Studies of the blood did not give evidence, therefore, that blood destruction was the factor concerned in the decrease in size of the heart in these animals. The presence of jaundice clinically, and of foci of cells in the microscopic sections of the organs after death which may have been regenerating red blood cells, however, suggests that a certain degree of blood destruction may have occurred.

*Effect of Diphtheria Toxin on the Capillaries*—The possibility that diphtheria toxin is a poison to the capillaries was mentioned. The toxin may cause dilatation of the capillaries similar to that caused by histamine, and the total increase in the vascular bed so brought about would result in a redistribution of the blood in the body—in a sense, draining it away from the heart. The heart would then become smaller, although the amount of blood in the circulation was the same. That there was a change in the capillaries is suggested by the frequent occurrence of ecchymoses at autopsy.

*Effect of Diphtheria Toxin on the Structure of the Heart Muscle—*

The gross and microscopic examinations of the hearts of the dogs that died of intoxication with diphtheria toxin have already been reported.<sup>1</sup> Lesions of the fibers of the heart muscle or of the interstitial tissues that could be attributed to the diphtheria toxin were not found. Therefore the decrease in cardiac area could not have been due to the actual destruction of muscle tissue.

*Effect of Diphtheria Toxin on the Weight of the Heart Muscle—*

There remains the possibility that the decrease in the size of the heart resulted from a loss of weight by the heart muscle itself. This was definitely exhibited in twelve dogs.

In dogs 81, 84, 86, 87, 97, 102, 103, 105, 107, 108, 110 and 112, there was a decrease in the ratio of the combined ventricular weights to the body weight (fig 9B). In these the heart muscle must have lost weight more rapidly than the body. If loss in both had proceeded at an equal pace, the ratio would have been undisturbed. In the other eight dogs, there might have been a decrease in heart weight, but in these the loss of weight by the body proceeded at a greater rate so that the  $\frac{L+R}{B \cdot W}$  ratio appeared greater than normal. This, however, did not preclude an absolute loss of weight by the heart muscle, although relative to the body weight this was not apparent. For this reason, the figures are misleading. This objection may be obviated in the following way. It may be assumed that, before the injection of the toxin, the weights of the hearts were such that  $\frac{L+R}{B \cdot W}$  would have a value approximating the average for normal dogs. If the body weight observed just before the injection of the toxin is used to calculate  $\frac{L+R}{B \cdot W}$  the weight of the heart at the time of death is seen to have decreased so that in all animals, except four (dogs 82, 83, 99 and 104), the heart did not weigh as much as it should have for a dog as large as the animals were before the injection. There was a tendency for the  $\frac{L+R}{B \cdot W}$  ratio to be lowest in those animals in which there was the greatest decrease in cardiac size (fig 9B). The  $\frac{L+R}{B \cdot W}$  ratios for all except the four dogs mentioned fell, then, below the average figure. These four dogs, however, showed large decreases in cardiac size and this mechanism cannot be called into play to explain them. The decrease in the L/R ratio (fig 9A) in all dogs, except dog 109, showed that there was some disturbance in the heart muscle that caused the left side of the heart to lose weight more rapidly than the right side, resulting in a change in the ratio of the two sides. The decrease in the amplitude of the R and R<sub>s</sub> waves (Stewart<sup>1</sup>) in the electrocardiogram also pointed to some disturbance in the muscle itself.

**Summary.** There was a decrease in the ratio of the combined ventricular weights to the body weight, which is most easily explained on the basis of a decrease in the weight of the heart. Parallel with this decrease in the weight of the heart there was a decrease in the size of the heart. This relationship is still more striking and the decrease in

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<sup>1</sup> The data from which figure 10 was constructed are contained in the first paper of this series.<sup>1</sup>



the weight of the heart can explain the decrease in size of the heart in all but four instances, if the ratio is calculated from the weight of the animal just before the injection of the toxin

By what mechanism, then, does the heart muscle lose weight? Nothing in the microscopic sections of the heart muscle indicated that an actual destruction of heart muscle cells had taken place. One is forced to look for some other mechanism by which the heart muscle could lose weight. Since there was not any destruction of muscle cells, it is possible that a loss of substances, such, perhaps, as fluid and salts

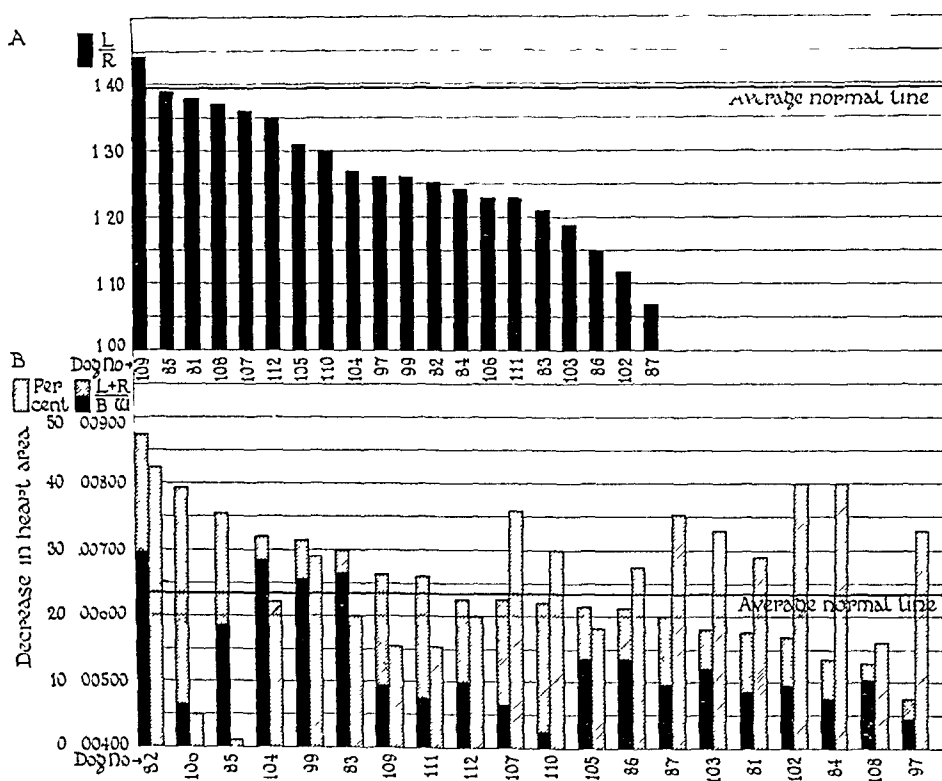


Fig 9—Graph A shows the grouping of the L/R ratios in dogs suffering from diphtheria intoxication with reference to the average L/R ratio in normal dogs. The height of the solid column represents the L/R ratio. Graph B shows the association between the change in the  $\frac{L+R}{B \cdot W}$  ratio and the decrease in cardiac area in dogs suffering from diphtheria intoxication. The total height of the left hand column represents the  $\frac{L+R}{B \cdot W}$  ratio when the weight of the dog at autopsy is used in calculating the ratio. The height of the solid column represents this ratio when the weight of the dog before the injection of diphtheria toxin is used in calculating this ratio. The height of the diagonally ruled area represents the decrease in cardiac area.

might account for the decrease in its weight and for the decrease in its size. Whether a change such as this actually occurred I cannot say, I am without evidence on this point.

## COMMENT

Following the injection of 0.00168 cc or more diphtheria toxin per kilogram of body weight into dogs, the cardiac area in the dogs, as measured in roentgenograms, decreased appreciably. It was found that 0.00135 cc of toxin per kilogram of body weight caused a similar change, but that 0.001 cc per kilogram did not. There was approximately the same decrease in body weight in all the dogs, an observation that precluded the possibility that the decrease in cardiac size was due to the decrease in body weight. Moreover, in dogs that had fasted for from three to four days, and in which there was a loss of body weight comparable to the loss of weight following diphtheria intoxication, there was no change in the size of the heart. This indicated that the decrease in cardiac size was due to the toxin. Counts of the red blood cells and estimations of the hemoglobin did not show evidence of marked destruction of blood. In these dogs, there was no consistent change in the total blood volume. In this connection, experiments showed that changes in blood volume are reflected in alterations in the size of the heart, in the following manner: A decrease in blood volume is accompanied by a decrease in the size of the heart and an increase in blood volume by a small increase in the size of the heart. The possibility that diphtheria toxin injures the capillaries was mentioned. A study of the  $\frac{L + R}{B \cdot W}$  ratios, however, pointed to the conclusion that there was a loss of weight by the heart muscle which could account for a part of, if not for all, the decrease in the size of the heart. This mechanism failed to explain the phenomenon in four instances. Histologic study of the muscle of the heart did not reveal an actual destruction of the cells of this muscle to account for the decrease in weight. There is a possibility that the latter was due to a disturbance in some mechanism involved in the maintenance of the water balance of the heart muscle cells. It may be that the decrease in the weight of the heart is not the only factor causing the decrease in size of the heart, the other possibilities mentioned may also play a rôle. Whatever the mechanism, it must take place rapidly, for the decrease in cardiac size was always well developed within twenty-four hours and was often at a maximum at that time.

## CONCLUSION

The injection of diphtheria toxin into a dog in a sufficiently large dose is followed by a decrease in the size of the heart. Analysis of the factors that may be involved in this alteration indicates that it is due to loss of weight by the heart, although other factors possibly play a part

# THE RETICULO-ENDOTHELIAL SYSTEM IN THE INFECTIOUS ANEMIA OF ALBINO RATS<sup>1</sup>

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The importance of the reticulo-endothelial system as a mechanism of defense in infectious diseases is generally recognized, although there are differences of opinion as to the functions and modes of action of the individual cells. The significant fact is that the body is normally equipped with a system of mobile cells of mesodermal origin which respond to infectious agents by proliferation, by migration and by differentiation into more active forms. Maximow,<sup>1</sup> in his recent review, has discussed the most commonly accepted views as to the rôle of the mesenchymal reactions in the general mechanism of defense. The studies of Metchnikoff<sup>2</sup> on the comparative pathology of inflammation furnish a biologic background in the conception that, in the simpler forms of animal life, the ameboid mesodermal cells are the active agents of intracellular digestion. After the differentiation of the entoderm, this function assumes a less prominent rôle, but persists and may become active in time of stress. Metchnikoff also believed that the antibodies, although of secondary importance in immunity, were formed by these mesodermal cells, but merely as a consequence of their property of phagocytosis and intracellular digestion.

These views of Metchnikoff did not attain general acceptance for many years, although various workers contributed facts of importance regarding the activities of these cells in individual organs, such as the liver and the spleen. Morphologic studies with the so-called vital staining methods gradually led to the conception of a system of such phagocytic cells, and since Aschoff<sup>3</sup> and Landau<sup>4</sup> gave the name of

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<sup>\*</sup> From the Department of Pathology and the Otho S. A. Sprague Memorial Institute, the University of Chicago

1 Maximow, A. A. The Morphology of the Mesenchymal Reactions, *Arch Path* **4** 557 (Oct) 1927

2 Metchnikoff, E. *Leçons sur la pathologie comparée de l'inflammation*, Paris, Masson & Cie, 1892

3 Aschoff, Ludwig. Das reticulo-endotheliale System, *Ergebn d inn Med u Kinderh* **26** 1, 1924

4 Landau, M. *Ber d Naturforsch Gesellsch zu Freiburg*, 1913, vol 20, cited by Aschoff (footnote 3)

reticulo-endothelial system to this aggregation of cells interest has been intensified in the activities of the system as a whole. Previously, the suggestion had been made that these cells, particularly in the spleen and the liver, were the active agents in the normal destruction and digestion of erythrocytes, and Kyes<sup>5</sup> named them hemophages with that idea in mind. Motohashi<sup>6</sup> later showed that in the rabbit this function is performed mainly in the spleen, to be assumed by the Kupffer cells of the liver and the macrophages of the bone marrow after the spleen is removed. It is probable that the phagocytosis of bacteria is merely a further adaptation of this general function of ingestion of particulate matter of various kinds.

In the present paper, we shall consider the reticulo-endothelial system as consisting in general, of all of the mesodermal cells of the body which are or may become endowed with the property of phagocytosis to a high degree. Although these cells are concentrated to the most marked extent in the spleen, liver, bone marrow, omentum, lymph nodes and lungs, they are probably distributed throughout all the connective tissues of the body. As Maximow has shown the importance of the lymphocyte as a potential macrophage, the entire lymphatic system should be considered as the biologic foundation of the reticulo-endothelial system.

Of all the individual organs of this system, the spleen ranks first in mammals, as the organ richest in histiocytes. But even here there appear to be differences between species as to the relative amount of reticulo-endothelial tissue in the spleen. Krumbhaar<sup>7</sup> has recently stated that the ratio of the weight of the spleen to that of the body indicates that the spleen is relatively of more significance in man, the dog and the rat, of less in the monkey and guinea-pig and of least in the cat and rabbit (fig. 1). It is suggestive that most of the earlier work on the effects of splenectomy on the production of antibodies was done with rabbits and guinea-pigs, animals in which the spleen quantitatively is of least significance. The conflicting results may well be explained in part by this. It would appear that in the study of the relative importance of the histiocytic functions of the spleen, the dog and the rat are better for use in experiments than are the monkey, the guinea-pig and the rabbit. As a matter of fact, the most convincing experiments as to the rôle of the spleen in the production of antibodies and in resistance to infection have been performed with the dog and the rat.

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5 Kyes, Preston. *Internat. Monatschr. f. Anat. u. Physiol.* **31**: 543, 1914.

6 Motohashi, Shinzo. The Effect of Splenectomy on the Production of Antibodies. *J. M. Research* **43**: 473, 1922.

7 Krumbhaar, E. B. Functions of the Spleen (Mysterium Plenum Organon). *Galen. Physiol. Rev.* **6**: 160, 1926.

(Bardach,<sup>8</sup> Hektoen,<sup>9</sup> Luckhardt and Becht,<sup>10</sup> Morris and Bullock,<sup>11</sup> Kritschewski and Rubinstein,<sup>12</sup> Lauda<sup>1</sup> et al) For example, Luckhardt and Becht found that splenectomized dogs did not produce hemolysins, hemagglutinins or hemopsonins as rapidly nor in as high concentration as normal dogs, and Hektoen, using rats, found the production of hemolysin markedly lowered after splenectomy. Bardach, in his work on anthrax, found that splenectomy in dogs led to a significantly higher fatality rate than was the case with normal animals. Morris and Bullock observed that the fatality rate in a large series of

■	Cat, 0.05%, (Krumbhaar)
■	Rabbit, 0.05%, (Krumbhaar)
■	Guinea Pig, 0.13%, (Krumbhaar)
■	Monkey, 0.13%, (Krumbhaar)
■	Dog, 0.25%, (Krumbhaar)
■	Wistar Rats, Normal, 0.26%, (Cannon, Donaldson)
	Bartonella Rats, 0.74%, (Cannon).
■	Man, Normal, 0.25%, (Krumbhaar)
■	Man, with splenomegaly, 0.75% (Spleen wt --525gms in a 70kg human.)

Fig 1—The relative ratios of the weight of the spleen to that of the body in various species, with comparison of the ratio for normal rats with that for *Bartonella*-infected rats and of the ratio for normal man with that of man with splenomegaly

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11 Morris, D. H. and Bullock, F. D. The Importance of the Spleen in Resistance to Infection Ann Surg **70** 513, 1919

12 Kritschewski, J. L., and Rubinstein, P. L. Immunity in Relapsing Fever 1 The Influence of the Reticulo-Endothelial System, Ztschr f Immunitätsforsch u exper Therap **51** 27, 1927

13 Lauda, E. Ueber die bei Ratten nach Entmilzung auftretenden schweren anämischen Zustände. 'Perniciöse Anämie der Ratten,' Virchows Arch f path Anat **258** 529 1925

splenectomized rats exposed to chance infection with so-called rat plague was much greater than with oichidectomized animals kept under similar conditions. These results indicate that in the case of animals in which there is a comparatively large amount of reticulo-endothelial tissue in the spleen, the removal of this organ leads to decreased production of antibodies and to decreased resistance to certain bacterial infections.

The demonstration that particulate matter and certain colloidal substances are selectively removed from the circulation led to the idea of saturating or "blocking" the cells of the histiocytic system, thereby reducing to a minimum their further powers of phagocytosis and of production of antibodies. Numerous attempts to produce this condition have been made, using particularly India ink and trypan blue, but here again the results have been extremely variable. In some instances, this variability has undoubtedly been due to an insufficient amount of the material injected, in others, to a failure to maintain the saturation during the period of observation. The positive results of Murata,<sup>14</sup> Gay and Clark,<sup>15</sup> Stewart and Parker,<sup>16</sup> Bieling and Isaac,<sup>17</sup> Siegmund<sup>18</sup> and others, however, point strongly to the conclusion that a blockade under proper conditions materially depresses the production of antibodies.

#### THE PART PLAYED BY THE SPLEEN IN THE DEFENSE MECHANISM OF THE RETICULO-ENDOTHELIAL SYSTEM

More recently, the method has been applied, particularly in conjunction with splenectomy, to animals infected with various organisms. Thus, Kutschewski and Rubinstein<sup>12</sup> found that, whereas the fatality rate in normal mice infected with *Spironema duttoni* is 3.82 per cent, in mice splenectomized three days after the infection the rate is 82.15 per cent, and in splenectomized mice into which a solution of iron saccharate has been injected to blockade the remainder of the reticulo-endothelial system, the death rate is 90.47 per cent. The

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14 Murata, M., quoted by Aschoff. Lectures on Pathology, New York, Paul B. Hoeber, 1924, p. 28.

15 Gay, F. P., and Clark, A. R. The Reticulo-Endothelial System in Relation to Antibody Formation, *Proc. Soc. Exper. Biol. & Med.* **22** 1, 1924, also *J. A. M. A.* **83** 1296 (Oct. 25) 1924.

16 Stewart, F. W., and Parker, Frederick, Jr. So-Called "Endothelial Blockade" with Collargol. An Immunologic and Histologic Study, *Am. J. Path.* **2** 381, 1926.

17 Bieling, R., and Isaac, S. Experimentelle Untersuchungen über intravitale Hamolyse. IV. Die Bedeutung des Reticulo-Endothels, *Ztschr. f. d. ges. exper. Med.* **28** 180, 1922.

18 Siegmund, H. Speicherung durch Reticuloendothelien, cellulare Reaktion und Immunität. *Klin. Wchnschr.* **1** 2566, 1922.

apparent lack of the formation of antibodies in relapsing fever in mice after blockade and splenectomy was demonstrated by Jungeblut<sup>19</sup>

In view of these facts, the so-called *Bartonella* infection of rats offers an unusual opportunity to study the functions of the reticulo-endothelial system as a whole by blockade methods, and in part, by splenectomy. Furthermore, the remarkable latency of this infection ensures the utilization of an animal naturally infected.

*Observations on the Effect of Splenectomy in Bartonella-Infected Rats*—The disease due to *Bartonella munitz* was first described by Lauda<sup>13</sup> as the infectious anemia of rats, occurring only after the removal of the spleen. In our laboratory, splenectomy in a large series of infected rats has invariably led to a rapidly developing anemia, usually within from five to nine days, which is frequently accompanied by hemoglobinuria. Coincidentally, the small coccobacillary bodies known as *Bartonella* organisms are to be seen on the erythrocytes after the staining with Giemsa stain. The surprising feature is that animals with this so-called *Bartonella* infection appear healthy, and the disease flares up only after removal of the spleen. Removal of one or both suprarenal glands, one or both testes, the thyroid gland, the omentum, or both cerebriums of the brain does not have this effect, in these same animals, splenectomy is followed by the development of the typical anemia.<sup>20</sup> Removal of from one third to one half of the spleen does not have any effect, removal of two thirds of the organ sometimes is followed by a milder grade of anemia. When the pedicle of the spleen is ligated and the organ excised and placed in the general peritoneal cavity, the anemia develops as with splenectomy, indicating the necessity of an intact blood supply to keep the virus under control.

*Observations on the Size of the Spleen and Its Histologic Character in Bartonella-Infected Rats*—A fact of great significance is the size of the spleen in infected animals as compared with normal, uninfected ones. We weighed the spleen at operation in eighty-eight rats infected with the *Bartonella* virus. The average ratio of the weight of the spleen to that of the body for these was 0.74 per cent. As shown in figure 1, this corresponds to a spleen weighing 525 Gm. in a human being weighing 70 Kg. In contrast with these figures, we have the average found by Donaldson<sup>21</sup> for eighty-seven normal rats, 0.26 per cent. Our figures for thirty-four splenectomized Wistar rats, ranging in age from 3 weeks

19 Jungeblut, C. W. Ueber die Beziehungen zwischen retikuloendothelialen System und chemo-therapeutischer Wirkung, Ztschr. f. Hyg. u. Infektionskrankh. **107**: 357, 1927.

20 Cannon, P. R., Taliaferro, William, and Dragstedt, L. R. Anemia Following Splenectomy in White Rats, Proc. Soc. Exper. Biol. & Med. **25**: 359, 1928.

21 Donaldson, H. H. The Rat. Data and Reference Tables. Memoirs of the Wistar Institute of Anatomy and Biology, no. 6, Philadelphia, 1924.

to 18 months, give an average of 0.25 per cent. The difference between the ratios of the weight of the spleen to that of the body in *Bartonella*-infected rats and normal, uninfected Wistar rats is so striking that we feel that it is frequently possible to determine by this feature alone whether or not the animal has had the *Bartonella* infection.

Histologically, we find indubitable evidence of the reactive tendency of the reticulo-endothelium of the spleen in the presence of the *Bartonella* virus. Spleens from normal, uninfected Wistar strain rats

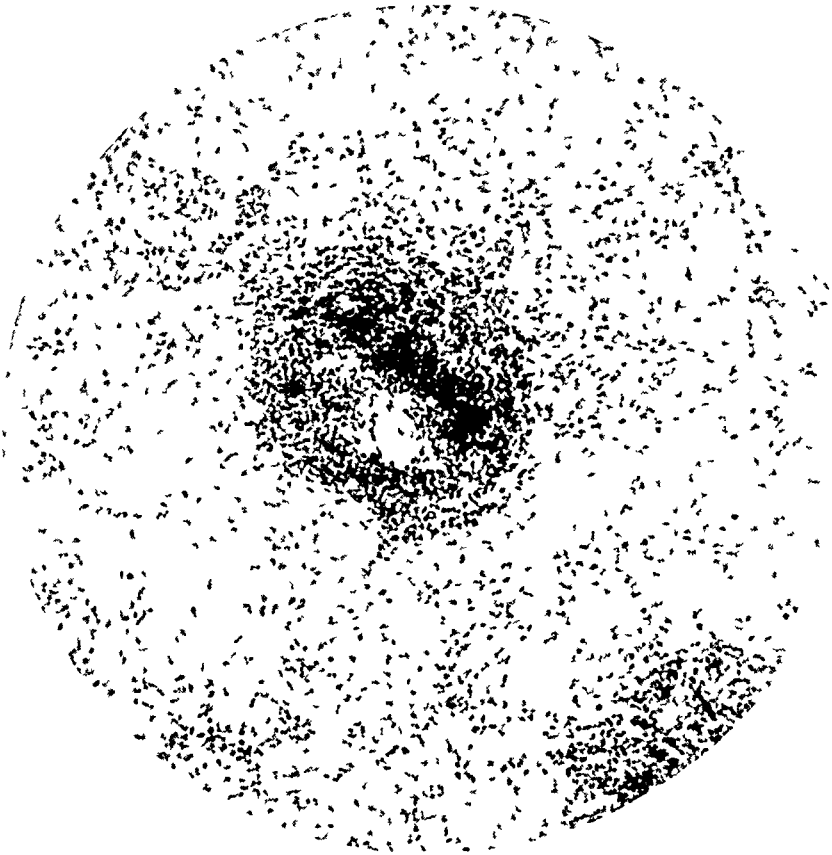


Fig. 2—Photomicrograph ( $\times 170$ ) of a splenic follicle in a normal rat. Note the compact collection of lymphocytes with a relatively narrow marginal zone.

are small and firm, the splenic follicles are compact, composed mainly of lymphocytes with only moderate evidence of hyperplasia of the centers of the follicles, and they have a relatively narrow marginal zone. On the other hand, spleens taken at operation from *Bartonella*-infected animals are large and fleshy. Microscopically, the splenic follicles are large with marked evidence of activity in the centers, as shown by numerous mitotic figures, and are surrounded by a broad marginal zone also containing many mitotic figures and hyperchromatic nuclei.



The picture is that of distinct hyperactivity and even hyperplasia of the reticulo-endothelial elements (figs 2, 3 and 4)

There can be little question, therefore, that the spleen acts in some manner to keep the *Bartonella* virus under control as a latent infection. When this inhibitive influence is removed, the virus apparently develops rapidly with the concomitant acute anemia. It is conceivable that the spleen, as an important part of the reticulo-endothelial system, may exert its controlling effect either by phagocytosis of the *Bartonella* virus

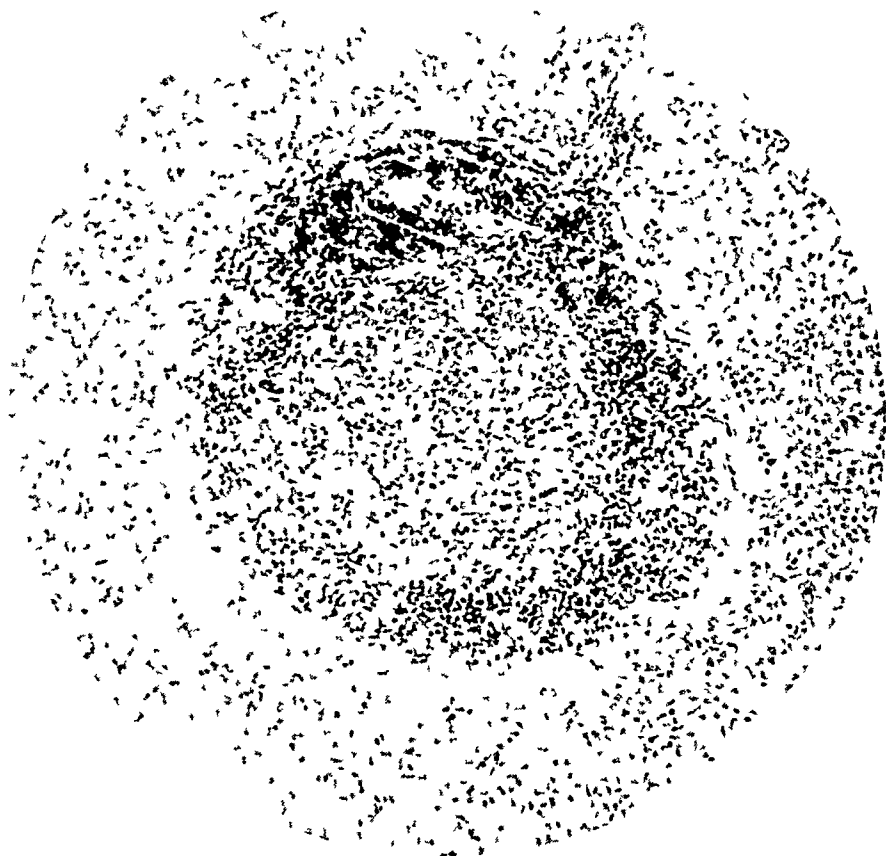


Fig 3—Photomicrograph ( $\times 170$ ) of a splenic follicle of a *Bartonella*-infected rat of the same age as the one shown in figure 2. Note the enlarged follicle with a prominent germinal center and a broad marginal zone.

at a constant rate or by the formation of antibodies of some type which restrain the development of or destroy the organisms or by both these processes. In any case, when the balance is disturbed between the offensive powers of the organisms and the defensive mechanisms of the host, the infection flares up and the anemia results. It is evident, then, that the "factor of safety" in the resistance to this infection resides in the spleen, equalling approximately two thirds of this organ, the removal of this factor allows the disease to progress.

EXPERIMENTS IN BLOCKADING THE RETICULO-ENDOTHELIAL SYSTEM  
OF SPLENECTOMIZED AND NONSPLENECTOMIZED RATS  
INFECTED WITH *BARTONELLA MURIS*

If the latency of this infection is the result of the defensive activities of the reticulo-endothelial system, a saturation of the cells of this system with particulate matter to as high a degree as possible should enable the *Bartonella* virus to gain the ascendancy with a resulting anemia and the reappearance of *Bartonella* bodies on the erythrocytes. Further-

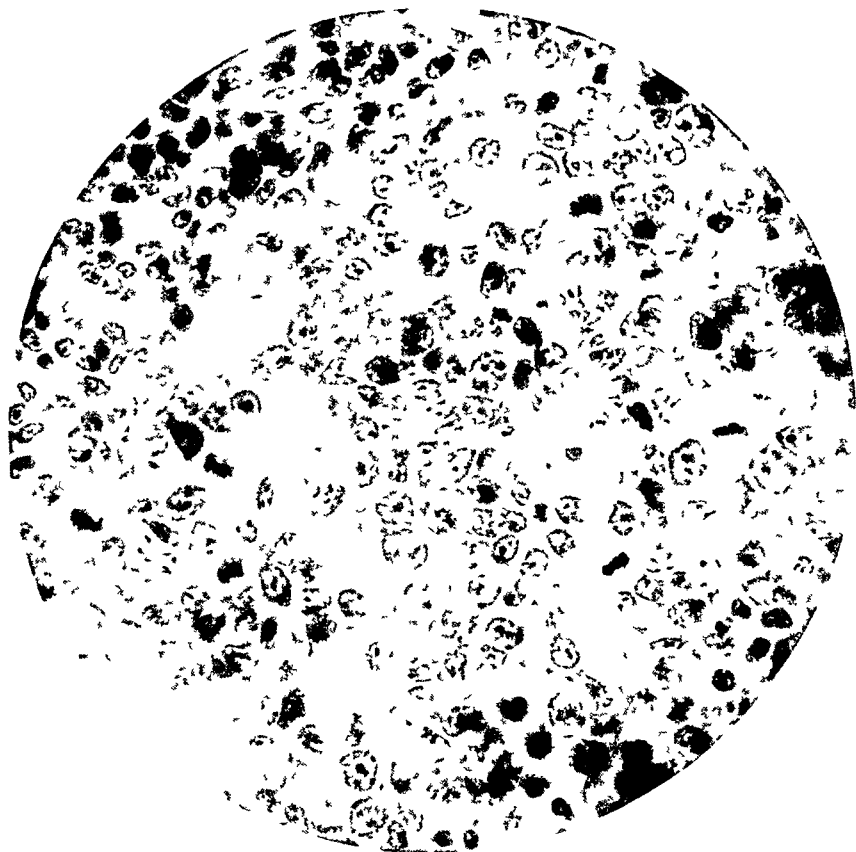


Fig 4—Photomicrograph ( $\times 650$ ) of the germinal center of the splenic follicles shown in figure 3. Numerous mitotic figures and hyperchromatic nuclei may be seen.

more, splenectomized animals that have recovered from the anemia should nevertheless have a lower factor of safety and thus should suffer a relapse after a blockading of the remaining elements of the histiocytic system.

*Method*—With that thought in mind, Higgin's india ink was prepared as a 4 per cent suspension in 0.85 per cent sodium chloride solution, filtered two or three times through no. 595 filter paper (Schleicher and Schull) and autoclaved. This was then injected intraperitoneally, in 10 cc amounts, at daily intervals, into three splenectomized *Bartonella* infected rats and three rats of the Wistar strain.

All had been splenectomized from one to two months previously, the former having had the typical infectious anemia and having returned to an approximately normal condition so far as the blood picture was concerned

*Series 1, Using Splenectomized Rats*—The injection of a total of 80 cc of the india ink led, in the case of *Bartonella*-infected rats, nos 111T, 112T and 130T, to a marked drop in the hemoglobin concomitantly with the reappearance of countless *Bartonella* bodies on the erythrocytes at the height of the anemia. The injection of the india ink into the splenectomized animals of the Wistar strain (nos 136T, 140W and 141W) did not have this effect, there being only a slight drop in hemoglobin values, although a larger total amount of ink was injected. Figure 5 illustrates the course of events in this series, and table 1 gives the amount of ink injected per gram of body weight for each animal. The moving average method has been used in figures 5, 6 and 7.

TABLE 1—Results of Blockading the Reticulo-Endothelium System of Splenectomized *Bartonella*-Infected Rats

Rats	Amount of Ink Injected, in Cc. of 1% Suspension, per Gm. Body Weight	Effect
111T}	0.27	Anemia
130T} <i>Bartonella</i> infected rats	0.51	Anemia
112T}	0.21	Anemia
136T}	1.06	No anemia
140T} Normal controls	0.82	No anemia
141T}	0.97	No anemia

Giemsa stains showed the blood picture in the uninfected animals to be essentially normal throughout the period of observation.

The experiments of Nagao<sup>22</sup> and Brickner,<sup>23</sup> using injections of india ink, showed that this material is taken up to a marked degree by the histiocytes of the reticulo-endothelial system. Presumably, in series 1, the phagocytosis of the ink particles by these cells so depressed their activities toward the *Bartonella* infection that a relapse occurred, at least, the blood picture was of the same type as that following splenectomy in these animals.

*Series 2, Using Nonsplenectomized Rats*—We next repeated the experiment, using four infected rats (nos 105T, 106T, 108T and 109T) the spleens of which had not been removed. The daily intraperitoneal injection, in 10 cc. amounts, of a 4 per cent suspension of india ink had only a slight effect, even after prolonged treatment. In rat 105T, there was a decline in hemoglobin from an initial value of 12.5 Gm. per hun-

<sup>22</sup> Nagao, K. The Fate of India Ink Injected into the Blood. I. General Observations, *J. Infect. Dis.* **27**: 527, 1920.

<sup>23</sup> Brickner, R. M. The Role of the Capillaries and Their Endothelium in the Distribution of Colloidal Carbon by the Blood Stream, *Bull. Johns Hopkins Hosp.* **40**: 90, 1927.

died cubic centimeters of blood to 7.9 Gm, together with a few suspicious looking *Bartonella* bodies on the erythrocytes. The continuance of the injections until 240 cc of the ink suspension had been injected did not cause the hemoglobin to go any lower. Similar results were obtained with rat 106T. After 170 cc of ink had been injected intraperitoneally the hemoglobin value had fallen from 13.5 Gm per hundred cubic centimeters of blood to 7.9 Gm and there was marked polychromatophilia, anisocytosis and an occasional normoblast in the blood smear. At no time, however, were definite bartonellas seen.

These results suggested that in order to get a "functional paralysis" of the reticulo-endothelial cells, one must saturate them to a maximal degree in a minimum of time in order to prevent proliferative activities of the histiocytes from interfering with the course of events. With this end in view, rats 108T and 109T were given injections intraperitoneally

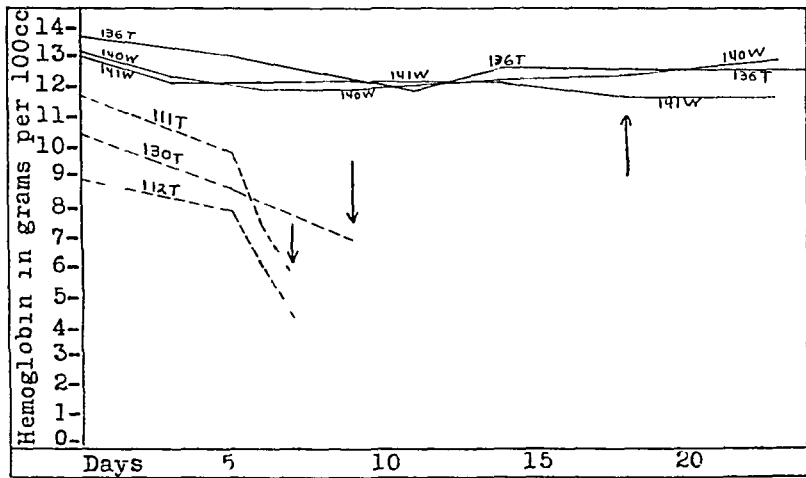


Fig 5—The straight line represents splenectomized Wistar rats, the broken line, Bartonella-infected rats. The graphs show the hemoglobin curves for three splenectomized Bartonella-infected rats that were given daily injections of a 4 per cent suspension of Higgin's india ink in 0.85 per cent sodium chloride solution. Injections were begun on the first day and were discontinued on the days indicated by the arrows.

of 60 cc of a 4 per cent suspension of india ink in sodium chloride solution, in 10 cc amounts twice daily, followed by daily intravenous injections of from 5 to 6 cc of the suspension of ink, for eleven days. During this period, the hemoglobin of rat 108T fell from 13.5 Gm per hundred cubic centimeters of blood to 5.2 Gm, with a rapidly increasing polychromatophilia and anisocytosis. At the lower reading, normoblasts appeared but definite bartonellas were not seen. The hemoglobin content of rat 109T dropped from 15.1 Gm per hundred cubic centimeters of blood to 7.6 Gm but here again definite bartonellas were not seen. Figure 6 shows the hemoglobin trend for these animals and table 2 gives the amount of the suspension of ink injected per gram of body weight.

It is interesting that the anemia was more marked in the animals getting the intravenous injections, although much less of the suspension of ink per gram of body weight was injected

*Series 3, with Maximal Saturation of Reticulo-Endothelial Systems of Bartonella-Infected Rats in Minimal Time*—The results of series 2 indicated clearly that an effective blockade of the histiocytic system demands maximal saturation in minimal time. Previous workers found that small amounts of injected material may stimulate rather than depress the activities of these cells. Furthermore, there is evidence that under this stimulation, an actual hyperplasia of the reticulo-endothelial system occurs. If the histiocytes secrete a substance that restrains the

TABLE 2—Results of Prolonged Injection of India Ink into Nonsplenectomized Bartonella-Infected Rats Compared with Results of Maximal Saturation in Minimal Time

Rat	Amount of Ink Injected, in Cc. of 4% Suspension, per Gm. Body Weight	Effect
105L	1.34 (prolonged period)	Moderate anemia
106T	1.44 (prolonged period)	Moderate anemia
108L	0.80 (minimal period)	Moderate anemia
109L	0.75 (minimal period)	Moderate anemia

TABLE 3—Results of Saturating the Reticulo-Endothelial Systems of Bartonella-Infected Rats with Intravenous Injections of India Ink

Rat	Amount of Ink Injected, in Cc. of 8% Suspension, per Gm. Body Weight	Effect
162 (normal control)	0.68	No anemia
132	0.63	Moderate anemia
163	0.65	Marked anemia
164	0.69	Marked anemia

development of the activities of the *Bartonella* virus, it is imperative that these cells shall be completely saturated and kept in a state approaching saturation.

Therefore, an 8 per cent suspension of Higgins India ink in 0.85 per cent sodium chloride solution was prepared as outlined heretofore. Three *Bartonella*-infected rats, nos. 132, 163 and 184, were given injections intravenously, twice daily, of from 5 to 6 cc. of the suspension of ink. At the same time Wistar strain rat 162 was similarly treated as a control. Figure 7 shows the hemoglobin curves and table 3 the amount of ink injected per gram of body weight.

The most significant feature in this series was the demonstration of the relatively enormous amount of the suspension of ink necessary to cause the severe anemia to appear. It is evident, then, that adequate blockade of the reticulo-endothelial system requires the intensive intravenous and intraperitoneal injection of large amounts of the blocking

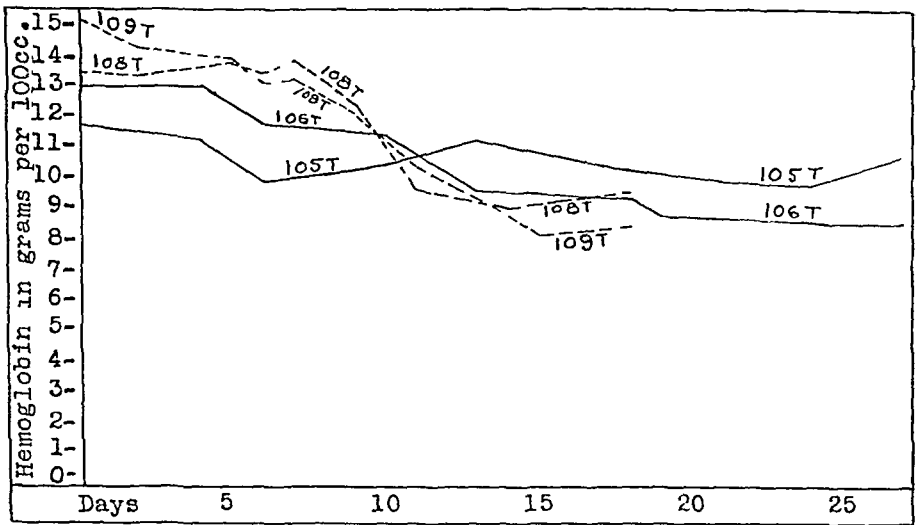


Fig 6—The graphs show the hemoglobin curves for four *Bartonella*-infected rats that were given injections of a 4 per cent suspension of Higgins' india ink in 0.85 per cent sodium chloride solution

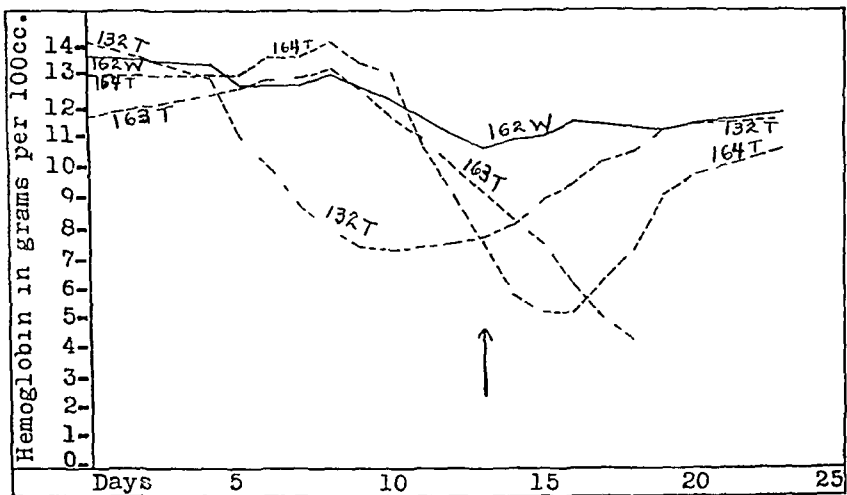


Fig 7—The straight line represents normal Wistar rats, the broken line, *Bartonella*-infected rats. The graphs show the hemoglobin curves for one normal Wistar rat and three *Bartonella*-infected rats that twice daily were given injections of an 8 per cent suspension of Higgins' india ink in 0.85 per cent sodium chloride solution. Injections were begun the first day, and were discontinued on the day indicated by the arrows.

material over a period of several days, in our series it took at least two weeks

#### COMMENT

The spleen has long been considered a mysterious organ, yet accumulating evidence consistently indicates its importance in the defensive struggle against bacterial agents. The splenic swelling in many of the acute and chronic diseases of bacterial and protozoan origin confirms this. This enlargement was thought by Goldzieher<sup>24</sup> to be due to an actual hyperplasia of the reticulo-endothelial elements of the spleen, being especially evident in typhoid fever, acute sepsis and malaria. He interpreted this as a defensive reaction of a purpuric nature.

The statement has been frequently made, even in recent literature, that the spleen is not essential to life. The significant question is: Is the spleen essential to life when the host is subjected to undue hazards? In other words, does not this organ represent a large "factor of safety" which, under abnormal conditions, may be the determining factor in resistance to infection? At such a time, splenectomy may decide the contest in favor of the infecting organism. This point has been particularly stressed by Morris and Bullock<sup>11</sup> and by Kikuth<sup>25</sup>. The recent review of splenectomies at the Mayo Clinic<sup>26</sup> indicates the same probability in conditions of acute infection.

Of wider biologic significance, however, is the rôle of the reticulo-endothelial system as a whole, of which the spleen is only a part. It would appear in view of the studies of Gay<sup>27</sup> and his students that the cells of this system are of more importance in streptococcus infections than was formerly believed to be the case. Without necessarily minimizing the value of the microphage as a cell of defense, the macrophage now assumes more significance.

The function of phagocytosis, possessed to a marked degree by the histiocytes, led to the attempts to "blockade" this system which have given such variable results. It is of interest that Bardach,<sup>8</sup> as early as 1889, injected a suspension of wood charcoal into dogs and then, later, anthrax bacilli, and found that the animals all succumbed to the infection in spite of the marked insusceptibility of the dog to anthrax. Although the more recent attempts to influence the production of antibodies have been relatively inconclusive, it must be remembered that there is a vast difference in the modes of procedure. For instance, it

24 Goldzieher, M. A. The Structure of Infectious Splenic Swelling, *Arch Path* **3** 42 (Jan.) 1927.

25 Kikuth, Walter. Studien zur Bedeutung der Milz als Abwehrorgan bei Infektionskrankheiten, *Klin Wchnschr* **6** 406, 1927.

26 Mayo, W. J. A Review of 500 Splenectomies with Special Reference to Mortality and End Results, *Ann Surg* **88** 409, 1928.

27 Gay, F. P., and Morrison, L. F. Studies in Streptococcus Infection and Immunity. V. Clasmatocytes and Resistance to Streptococcus Infection, *J Infect Dis* **33** 338, 1923.

cannot be merely assumed that the system is "blocked", histologic examinations must be made in order to prove it. The injections should be made intravenously, for, as we have found, daily intraperitoneal injections of relatively enormous amounts of a suspension of india ink over a period of thirty days may result in but minimal quantities of ink in the bone-marrow. It is probable that these intraperitoneal injections soon lead to a proliferation of the peritoneal mesothelium, so that little of the ink injected later is absorbed. This may explain why, after such injections into the *Bartonella*-infected animals, the maximal anemia appeared within a few days, followed by a gradual improvement in spite of the continued daily injections of the suspension of ink.

These observations may be of significance in connection with some other conditions in which there is evidence of hyperactivity and hyperplasia of the spleen. For instance, splenectomy in pernicious anemia was suggested by Eppinger on the hypothesis that there is a "hyper-splenism" of unknown cause. It is more probable however that in most of the infections and anemias in which the spleen is enlarged this enlargement is secondary rather than primary. In the present instance we have physiologic and morphologic evidence that the hyperactivity and hyperplasia of the reticulo-endothelial elements of the spleen are compensatory mechanisms of defense, the splenomegaly thus being the consequence rather than the cause. Removal of this mechanism allows the virus to develop relatively without restraint and the infectious anemia results.

#### SUMMARY AND CONCLUSIONS

The removal of the spleen in albino rats infected with the virus of so-called *Bartonella muris* leads to the development of an acute anemia, the infectious anemia of rats.

The removal of such other organs as the suprarenal glands, the testes, the omentum, the thyroid gland or the cerebrum does not have this effect. In these same animals, the later removal of the spleen causes the anemia to appear.

The enlarged spleens in such animals are the result of hyperactivity and hyperplasia of the reticulo-endothelial elements, this being a compensatory mechanism of defense.

Adequate blockade of the entire reticulo-endothelial system with india ink in *Bartonella*-infected rats is followed by the development of an anemia of the same type as that following splenectomy.

The reticulo-endothelial system in general, and the spleen in particular, restrain the development of the *Bartonella* virus and establish the latency of the infection, interference with this system, either by ablation or by saturation of the phagocytic cells with particulate matter, allows the virus to develop unduly with the resultant infectious anemia.

The "factor of safety" in this defensive mechanism is in the spleen, the removal of this factor is followed by a recurrence of the infection.



# SICKLE CELL ANEMIA

## FURTHER INVESTIGATION OF A CASE OF SPLENIC ATROPHY WITH CALCIUM AND IRON INCRUSTATIONS (NODULAR SPLENIC ATROPHY) ^

G A BENNETT, M D

LOS AN

In a recent publication<sup>1</sup> I reported observations, from the necropsy material of a negress, aged 20, on an unusual spleen which weighed 10 Gm and which showed microscopically the presence of calcium and iron incrustations in the walls of blood vessels and in the fibrous and elastic tissues of the trabeculae. No relationship between the atrophic spleen and the patient's acute illness seemed warranted though her death during the engorgement stage of a bilateral lobar pneumonia seemed most unusual. The following conclusions were drawn in commenting on the possibilities in the previous report: "It seems that because of the iron in isolated fibers and in areas of considerable size without the presence of calcium the iron was of primary importance. It also seems that there was some etiologic factor either in hemorrhage or in necrosis, or possibly in both, to cause the deposition of such a large amount of iron."

My attention has since been called to the possibility that the entire splenic condition might have been explained on the basis of sickle cell anemia<sup>2</sup>. For this reason the necropsy material and the clinical record were reexamined. Examination of the blood during life showed a hemoglobin value of 65 per cent (Tallqvist), red cells 3,040,000 and white cells 38,000 per cubic millimeter. The stained smear showed variation in size and shape with some polychromatophilia and fragmentation of the red cells. There were four reticulated cells seen. The differential count was: polymorphonuclears, 87 per cent, large mononuclears, 7 per cent, lymphocytes 5 per cent, and basophils, 1 per cent. Smear preparations made from intravascular blood clots of tissues fixed in 10 per cent

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From the Department of Pathology of the Peter Bent Brigham Hospital and Harvard Medical School

1 Bennett, G A. Splenic Atrophy with Calcium and Iron Incrustations (Nodular Splenic Atrophy), Arch Path 7:71 (Jan) 1929

2 Bernhard Sternberg M D, Toledo, Ohio, and G S Graham M D, Birmingham Ala

formaldehyde revealed nearly 100 per cent sickle cells (fig 1), while similarly prepared and treated smears from control cases showed red blood cells of normal contour (fig 2). Graham<sup>3</sup> and later Hahn and Gillispie<sup>4</sup> observed that sickle cell distortion could be seen in sections of formaldehyde hardened tissues from affected subjects, whereas the red blood cells were not sickled in tissues fixed in Zenker's fluid.

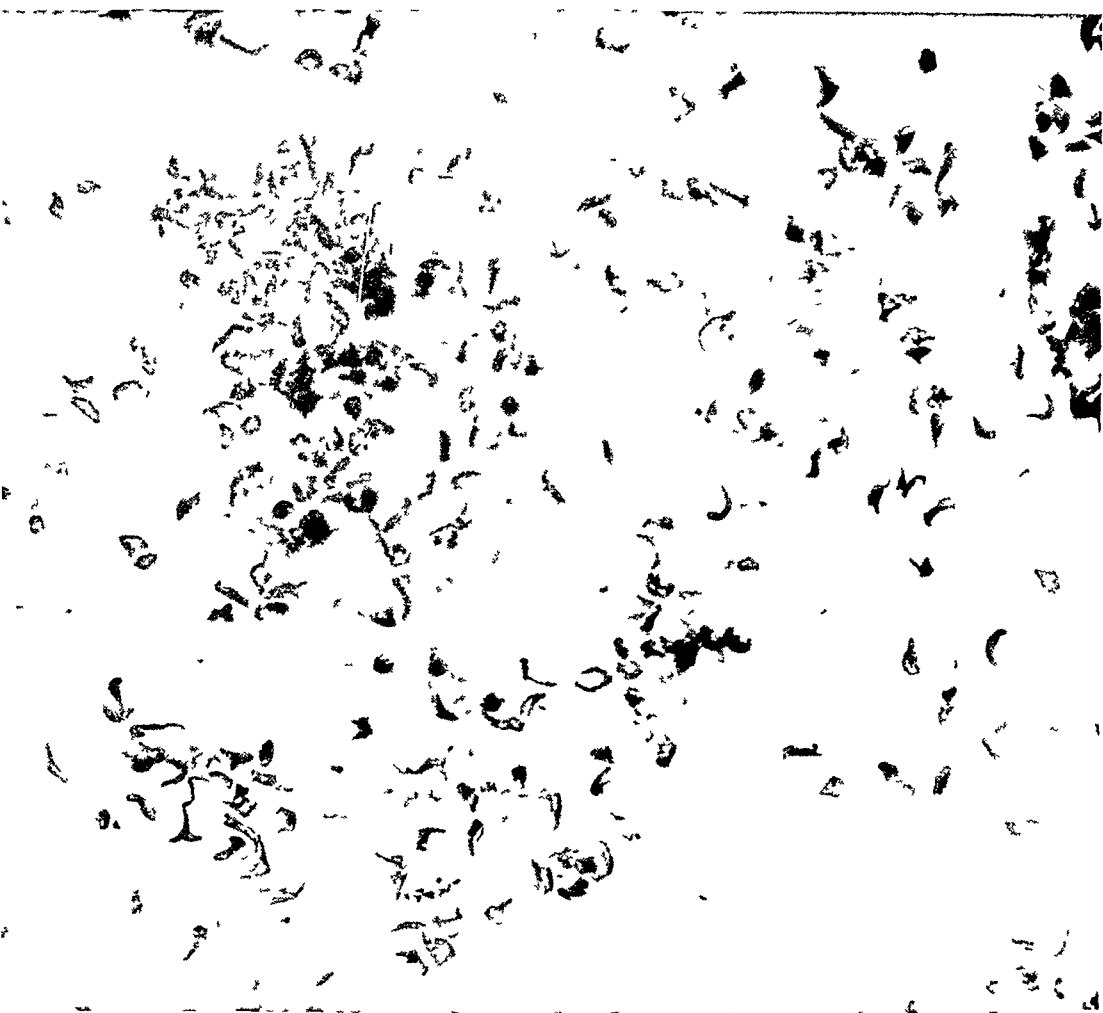


Fig 1—Nearly complete sickle cell distortion as seen in smears from blood clot fixed in formaldehyde

It is worth while noting that a recent examination of the blood of the mother, who is the only living relative, showed none of the sickle cell traits, and there was no anemia.

3 Graham, G. S. A Case of Sickle Cell Anemia with Necropsy, *Arch Int Med* **34** 778 (Dec) 1924

4 Hahn, E. V., and Gillispie, E. B. Sickle Cell Anemia, *Arch Int Med* **39** 233 (Feb) 1927

## SUMMARY

The case previously reported because of an unusual atrophic spleen with calcium and iron incrustations should undoubtedly be regarded as a case of sickle cell anemia

Sickle cell anemia may be recognized from necropsy material by crushing blood clot from tissues hardened in 10 per cent formaldehyde

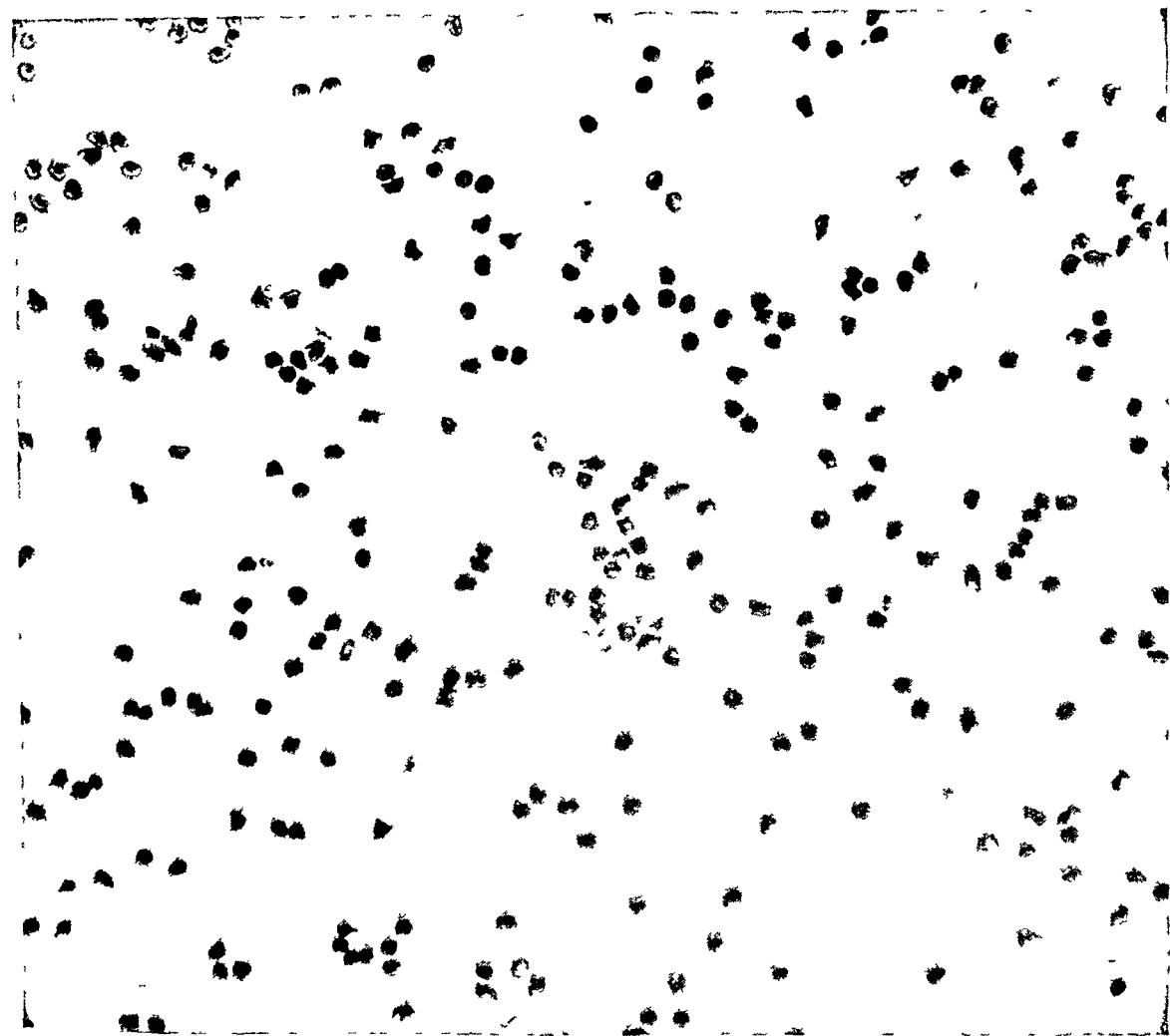


Fig 2—Red blood cells as seen in control smears from unaffected subjects. Note the preservation of the cell shapes after two years' fixation in 10 per cent formaldehyde. Method of preparation of figures 1 and 2 was identical.

in physiologic solution of sodium chloride and making smear preparations from the resultant suspension. The elapse of time after fixation seems to be of no importance in the amount or character of the red cell distortion.

# THE EFFECT ON THE WHITE BLOOD CELLS OF INTRAPERITONEAL INJECTION OF WHOLE LIVER\*

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AND

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Previous observations have established a relationship between certain forms of hepatic disorder and the number of mononuclear cells in the circulating blood. Jones and Minot<sup>1</sup> observed both a relative and an absolute increase in the number of monocytes in the blood in patients with catarrhal jaundice. More recently Thewlis and Middleton<sup>2</sup> studied the blood in thirty-eight cases of this condition and described similar changes. The essential observations of the latter investigators were a leukopenia, a marked decrease in the number of polymorphonuclear cells, a moderate decrease in that of lymphocytes and an increase in that of monocytes. A somewhat similar observation was reported by Minot and Smith<sup>3</sup> for occupational tetrachlorethane poisoning, in which there was an increase in the number of monocytes in the blood stream. The effect of actual degeneration of the liver on the monocytes was studied by Holt<sup>4</sup> who ligated one of the hepatic ducts and found that this operation was followed by a rise in the monocyte count.

In these three conditions, catarrhal jaundice, tetrachlorethane poisoning and ligation of a bile duct, a rise in the monocyte count and injury to the liver were always present. Since the increase in the number of the monocytes occurred with injury to the liver, it seems possible that the increase is a direct result of the injury. It is obvious that if this hypothesis is correct the mechanism involved may be one of several. The injury to the liver may bring about a change in its physiologic activities

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Submitted for publication Dec 10, 1928

From the Departments of Anatomy and Medicine, Vanderbilt University School of Medicine

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1 Jones C M, and Minot, G R. Infectious (Catarrhal) Jaundice. An Attempt to Establish a Clinical Entity. Observation on the Excretion and Retention of the Bile Pigments and on the Blood, Boston M & S J **189** 531 1923

2 Thewlis, Ethel, and Middleton, W S. The Leukocytic Picture in Catarrhal Jaundice (Cholangitis), Am J M Sc **169** 59, 1925

3 Minot G R and Smith, L W. The Blood in Tetrachlorethane Poisoning Arch Int Med **28** 687 (Dec) 1921

4 Holt R B. Effect on White Blood Cells in Rabbit by Ligation of Common Bile Duct, Proc Soc Exper Biol & Med **24** 974 1927

which, in turn, affects the balance in the production of blood cells. Again as the result of the degeneration, substances may be set free in the liver which affect the production of monocytes. For example, bilirubin, bile salts, cholesterol unsaturated fats or other substances may be set free under these conditions and may produce monocytosis by their effect on tissues elsewhere. In view of these considerations, it seemed worth while to investigate the monocyte by studying some of the possible relationships of this cell to liver tissue. It was decided, as the first step in such an investigation, to inject fresh normal liver into animals in order to determine whether this simple procedure would also cause a rise in the monocyte count. Accordingly, a suspension of fresh rabbit liver was injected into a series of rabbits and the effect on the blood noted.

#### EXPERIMENTAL PROCEDURES

This series included eleven rabbits. These may be divided into three groups. Group 1 includes five animals (nos 16, 17, 18, 19 and 21) all of which were carefully examined at autopsy for the presence of infections, and only one of which (no 17) showed any infectious process. This animal had questionable small pneumonic patches in the lungs. All these animals received injections of whole liver. Group 2 includes three animals (nos 2, 5 and 11). Rabbits 11 and 5 received injections of whole liver. Rabbit 2 received an injection, first of whole liver and then of perfused liver. None of the animals in this group was controlled by postmortem examination. Group 3 includes three animals (nos 8, 9 and 15), in all of which peritonitis was disclosed at autopsy. Two of these animals (nos 9 and 15) received injections of perfused liver.

The preparations of the whole liver were made as follows. A rabbit was killed with ether anesthesia and the liver immediately removed under aseptic conditions. This was either run through a meat chopper or macerated with mortar and pestle and a saline suspension of it was made. This suspension was strained through gauze and was then injected intraperitoneally. About one half of the suspension from one liver was injected into a single animal, the total volume being approximately from 25 to 30 cc.

The preparations of perfused liver were made as follows. The animal was killed by ether anesthesia and the abdominal cavity opened. A glass cannula was inserted into the hepatic artery, and a large volume of warm sterile physiologic sodium chloride solution was run through the liver. When all the blood had been washed out, the organ was removed and macerated and the suspension made as described.

Total and differential counts were made on all the animals for a period prior to the injection in order that the normal values of these counts might be established. Following the injection total and differential counts were made daily on all the animals for a period of approximately five days. On five animals (nos 16, 17, 18, 19 and 21), two counts were made daily for the first two days following the injection. In making the differential counts, the supravital technic was used with neutral red as the stain.

In addition to the three groups of rabbits mentioned, two other groups of three each were studied. The animals of one of these groups received injections of autoclaved calf liver, while those in the other series received injections of a suspension of calf liver prepared as described, but not heated or otherwise sterilized.

although every possible precaution was taken to prevent the liver's being contaminated Peritonitis developed in all these animals

RESULTS

In every instance, the animals in group 1 showed a definite rise in the number of monocytes in the circulating blood in from twenty-four to forty-eight hours after the injection of whole liver into the peritoneal cavity In three of the animals this rise was maintained for six days, and in the other two for three days Rabbit 16 showed the highest peak for the monocyte counts thirty-six hours after the injection of liver intra-peritoneally The absolute number of monocytes at this time was 3,257,

Average Blood Cell Counts of Rabbits Before and After Intraperitoneal Injection of Liver

Rab bit No	Neutrophils			Lymphocytes			Monocytes			Remarks
	Before	After	Average Difference in per Cent	Before	After	Average Difference in per Cent	Before	After	Average Difference in per Cent	
16	7 640	6 487		4 781	2,662		1,168	1 540		Group 1 All of this series were free from infections, except rabbit 17, which showed questionable small pneumonic patches
17	4,776	5,864		2,039	2,053		836	1 379		
18	4,614	4,333		2 907	2 184		1 029	1,024		
19	4,029	5 982		2,023	1,939		786	1 072		
21	4,404	6,449		1,866	1,499		439	1 288		
Aver	5,093	5 823	+14 3	2,723	2,067	-24 1	852	1,261	+48 0	
11	9 443	3 068		3 073	2,520		648	921		Group 2 This series was not controlled by autopsies, rabbit 2 received an injection first of whole liver and later of perfused liver, A indicates after whole liver, B, after perfused liver
5	4 984	3,387		2,446	2 300		143	780		
2	4 193	A5,591		3,764	A2,620		654	A1,209		
		B5,034			B1 636			B1,419		
Aver	6 207	44,015	-35 3	3 094	A2,480	-19 8	582	A 970	+66 7	
		B3,830	-38 3		B2 152	-30 4		B1,040	+78 7	
8	4 395	4 135		2 840	2 260		218	1,392		Group 3 Peritonitis was present in all of this series
9	5 965	2,126		2,401	1 188		1,140	971		
15	4,085	4 721		3 505	2 843		699	1 415		
Aver	4 815	3,661	-24 0	2 932	2,097	-28 5	682	1,259	+84 6	

whereas the average value before injection was 1,168 There was an associated slight increase in the total number of white blood cells the count being 13,560 The lowest maximal value for monocytes in this group was 1,810, in rabbit 19 The average monocyte count prior to the injection of liver in this animal was 786, and the total number of white blood cells was 13,400

There was a general tendency of the lymphocytes in this group to decrease in number following the injection, the average value after injection being 24 1 per cent below the average value before injection. The neutrophils showed a slight increase in numbers following the injection of liver

In group 2, the same type of reaction as regards the monocytes following the injection of liver was observed, the average increase being

66.7 per cent, which was slightly greater than that in group 1. Rabbit 7 received, first, an injection of whole liver and later one of perfused liver. Following the injection of whole liver, there was a marked temporary rise in the monocyte count to 5,140 with a total white blood cell count of 11,680. The average number of the monocytes during the period of seven days between the injections of whole and of perfused liver was 970. Following the injection of the perfused liver there was no great increase in the number of monocytes, but the curve had a slightly higher level, the average being 1,040. No real difference in the response of the lymphocytes in this group from that in group 1 was observed. The neutrophils, however, showed a definite decrease in number, but this was due to a marked decrease in the number of these cells in rabbit 11. In the other two animals of this group, the curve was somewhat higher after, than it was before, the injection.

In group 3, the animals all had peritonitis, and the only change in response to the injection of liver, as compared with the response in group 1, was a greater increase in the percentage of monocytes (84.6 per cent). However, marked peaks did not occur, and the average absolute value of the monocytes was not high (1,259). It was practically the same as that for group 1 (1,261).

#### COMMENT

The one outstanding result in this series of experiments was the definite increase in the number of monocytes following the injection of a suspension of liver into the peritoneal cavity. This was a constant observation, and it occurred within from twenty-four to forty-eight hours after the injection. The explanation of this increase is not obvious. Several possibilities present themselves. The simplest explanation is that the increase was due to the degeneration of the liver tissue in the peritoneal cavity with the liberation of some stimulant active in the production of monocytes. Again, it might have been due to the action of the liver, or substances formed from it by chemical changes, on the peritoneum or other tissues locally—i.e., it might have been a kind of foreign body reaction. The third possibility is that the degenerated liver produced substances which, in turn, acted on the liver cells of the animal and brought about the condition that stimulated the production of monocytes.

Of interest is the early marked decrease of the number of monocytes and lymphocytes, with an inconstant reaction of the neutrophils. The monocytes remained decreased in number only for a short period and then increased, whereas the lymphocytes showed an average decrease of 24.1 per cent throughout the period of observation following the injection of liver. So far as this series of experiments goes, it seems

that the factor producing monocytosis was capable of causing a diminution in the number of lymphocytes. Is it possible that the two types of cells are mutually inhibitory?

The changes in the animals with frank peritonitis were different from those in the animals of group 1 in two respects. First, the neutrophils were decreased in number, rather than increased, their average total number after the injection being 24 per cent below their average before injection. Second, the average increase in the percentage of the monocytes was distinctly higher than it was in the group of noninfected animals. May we assume that the number of the monocytes was increased as a result of this infection alone, or was this increase the result of infection in a "sensitized" animal? In other words, is it possible that the number of the monocytes was elevated as a result of some change in the animal following the injection of liver whereby it was more able to produce monocytes in the presence of infection than normally? The decrease in the number of neutrophils is not the ordinary response to purulent infection, but it may be that this was due to massive infection. If so, one would expect the number of monocytes also to be decreased. The same type of reaction occurred when the suspension of calf liver was injected into the animals, in which again peritonitis was present. Autoclaved calf liver, when injected intraperitoneally, did not produce any change of note in the blood counts.

#### CONCLUSIONS

Rabbits into which rabbit liver has been injected intraperitoneally show in the blood, first, an initial decrease in the number of lymphocytes and of monocytes and later a decided increase in the number of monocytes with continued diminution in the number of lymphocytes. The number of neutrophils is slightly increased.



# FATTY CHANGES IN THE KUPFFER CELLS IN THE LIVER OF THE GUINEA-PIG IN PHOSPHORUS POISONING \*

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In the course of an investigation on the effect of phosphorus on the white cells of the blood of the guinea-pig, routine histologic examination of the liver revealed an increased amount of fat<sup>1</sup>. This fat seemed to be largely in the Kupffer cells and this uniformity of distribution suggested the extension of these experiments to a larger series of animals.

Eighty guinea-pigs were studied in this connection. Forty of these animals were controls and forty received phosphorus, either subcutaneously or by mouth. Of the forty animals that received phosphorus, twenty-eight were given subcutaneous injections of from 0.5 to 1 mg of yellow phosphorus in oil, repeated at intervals of from three to five days, until each animal had received from 1.5 to 5.5 mg in all. The other twelve animals were each given repeated doses of from 1 to 2 mg of phosphorus by mouth, for from six to thirteen days.

The interval of time elapsing between the administration of phosphorus to an animal and the postmortem examination varied widely, the shortest interval being two days and the longest thirty-nine days. Some of the animals died, but the great majority were put to death. Specimens of the livers were fixed in a diluted solution of formaldehyde U. S. P. (1:10), and frozen sections were cut and stained in hematoxylin and scharlach.

## RESULTS

Fourteen, or one half, of the animals receiving phosphorus subcutaneously had an accumulation of fat in the liver. Twelve of the animals showing fatty changes had a definite arrangement of the fat. In these animals, the fat showed a decided preference for the Kupffer cells, thus giving the section the appearance of a network of fat. Four of the guinea-pigs that had fat in the Kupffer cells also showed some fat in the

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<sup>1</sup> Huffman, M. M., Lawrence, J. S., and Jones, Edgar. The Effect on the White Blood Cells Produced by the Intraperitoneal Injection of Whole Liver Arch. Path., this issue, p. 804.

hepatic cells In these four, the periportal areas showed an accumulation of fat in all the Kupffer cells and in some of the hepatic cells As one approached the center of the lobule, an area was found in which only the Kupffer cells showed fatty globules, and finally, on reaching the cells in the immediate neighborhood of the central vein, fat was not found There were, then, three distinct zones as regards the accumulation of fat, viz, a periportal zone with fat in both the hepatic and the Kupffer cells, a middle zone with involvement of the Kupffer cells alone, and a central zone without fat in any of the cells The globules of fat tended to be of moderate size, the average size being considerably less than that of the nuclei The other two animals that showed positive signs of changes in the liver did not present this arrangement In one there was a diffuse involvement with fat,\* which was present in considerable amounts However, the central areas, in general, seemed to be spared The fat globules varied in size from some with a diameter equal to that of the nuclei to others like small particles In the other animal there was only a small excess of fat This was not located particularly in the Kupffer cells, but chiefly in the liver cells A preference was not shown for either the periportal or the central areas The globules of fat, on the average, were of the size of the nuclei The epithelium of one of the bile capillaries showed a small amount of fat The other fourteen animals into which subcutaneous injections of phosphorus had been made, did not show any evidence of an increase of fat in the liver by the technic used, viz, frozen sections of tissue fixed in a diluted solution of formaldehyde, U S P (1:10) and stained with scharlach 1

Of the twelve animals given phosphorus by mouth, only two failed to show an accumulation of fat in the liver Of those showing fatty changes, four showed a decided tendency for the fatty globules to appear in the Kupffer cells, six did not show this arrangement of the fat All these animals had an extensive accumulation of fat, both the hepatic and the Kupffer cells containing an excess of the fatty globules The general tendency was for the central area to be spared, three animals definitely showing this arrangement of the fat Two of the animals treated with phosphorus by mouth did not show fatty changes in the liver

There was a general tendency throughout the group of animals treated with phosphorus, and showing fatty changes, for the central areas to be spared at the expense of the periportal areas The epithelium of the bile capillaries contained a remarkably small amount of fat In only five of sixteen animals (approximately one third) particularly studied with reference to this point was there any accumulation of fat in the biliary epithelial cells, and in these there was only a small amount

## COMMENT

The great predilection of the fatty globules for the Kupffer cells is worthy of note. Twelve of fourteen animals showing fatty changes in the liver as a result of phosphorus poisoning presented this predilection. The occurrence was so regular that it does not seem that it can be questioned. It may be noted that a much higher percentage of the animals given phosphorus by mouth showed fatty changes of a more generalized nature. Eleven of the animals showing this generalized fatty degeneration had an extensive degenerative process in the liver. In consideration of the data presented—the typical and regular arrangement of the fat in the Kupffer cells, the lesser degree of fatty involvement in these animals, the wavelike arrangement of the fat in four guinea-pigs and, finally, the generalized involvement, with implication of both the Kupffer and the hepatic cells, but with a tendency to spare the central areas—it seems plausible to assume that one of the earliest changes in phosphorus poisoning is an accumulation of fatty globules in the Kupffer cells of the periportal areas. The next step, as regards the fat, is probably an involvement of Kupffer cells in the middle zones and the hepatic cells in the periportal areas. Later, the Kupffer cells in the central area are involved and the hepatic cells of the middle zones. Finally, all the zones and all the cells are involved. In other words, the process advances from periphery to center and from Kupffer cell to hepatic cell.

Questions arise as to the significance of the fat in the Kupffer cells. 1 Does the fat accumulate in these cells as the result of a lipemia and the secondary phagocytosis of the fatty droplets? 2 Is the appearance of fat merely a matter of changes in its character such that it can be shown by staining? In other words, is there no increase in the actual amount of fatty material in the cells but a change in the character of the fat, so that it stains with scharlach r, whereas, before this change, it did not stain in this way? 3 Is the fat that appears in the Kupffer cells the result of degeneration of the cytoplasm itself wherein fat is formed by changes of a chemical character involving the destruction of the cell cytoplasm? Our evidence does not thus far permit any answer to these questions. In this connection, it is of interest to consider the possible relationship between the involvement of the Kupffer cells and the increase in the number of monocytes in the circulating blood in animals treated with phosphorus subcutaneously. That the increase in monocytes is not always dependent on fatty infiltration of the Kupffer cells has been shown by Lawrence and Huffman.<sup>2</sup> However, fatty changes in the Kupffer cells may have been present in some

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<sup>2</sup> Lawrence, J. S., and Huffman, M. M. An Increase in the Number of Monocytes in the Blood Following Subcutaneous Administration of Yellow Phosphorus in Oil, *Arch. Path.*, this issue, p. 813.

of the animals showing increased numbers of monocytes in the blood at the time of the increase, and these may have disappeared later, since, as has been known for a long while, animals show fatty changes in the liver early in phosphorus poisoning, which may later disappear<sup>3</sup>

The large volume of recent work concerning the question of the relationship between the monocyte and the clasmatocyte renders it necessary to raise the question whether the changes in the Kupffer cells that took place following the administration of phosphorus could be a direct cause of the monocytosis occurring in these animals<sup>2</sup> The evidence in our series of experiments argues against any such direct connection, since none of the monocytes in the circulating blood contained fat and none of them, furthermore, were in any way similar to the Kupffer cell as examined free from the liver on fresh supravital smears On the other hand, our results do not permit definite statement regarding the question of the relationship between these two types of cells This question has been thoroughly discussed elsewhere<sup>4</sup>

The failure of sixteen of the forty animals to show any fatty changes in the liver should be noted In these animals, the average number of days elapsing after the administration of phosphorus was 15.3 against 8.8 days for those showing fatty changes The average total dosage of phosphorus for these animals was 2 mg, while that for the animals showing a typical accumulation of fat in the Kupffer cells was 21 mg These facts seem to indicate that the animals in this group were less susceptible to phosphorus than the others However, the explanation of the difference in reaction may be found in the failure of absorption of the material from the subcutaneous tissue in certain of the animals Normally, the liver of the guinea-pig contains only a small amount of fat In our group of forty control animals, the liver in only one case showed more than the faintest demonstrable trace of fat

#### CONCLUSION

Administration of phosphorus in small amounts to guinea-pigs produces an accumulation of fatty globules in the Kupffer cells as an early manifestation of phosphorus poisoning of the liver

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3 Oppel, Albert Kausal-morphologische Zellenstudien I Ueber totale Regeneration des Leberzellennetzes nach Phosphorvergiftung und uber dabei stattfindende Anpassungs- und Auslesevorgange, *Med-naturw Arch* **2** 61, 1908

4 Cunningham, R. S., Sabin, F. R., and Doan, C. A. The Development of Leukocytes, Lymphocytes and Monocytes from a Specific Stem-Cell in Adult Tissues, *Contrib Embryol Carnegie Inst, Washington* **16** 227, 1925 Sabin, F. R., and Doan, C. A. The Presence of Desquamated Endothelial Cells, the So-Called Clasmatocytes, in Normal Mammalian Blood, *J Exper Med* **43** 823, 1926

# AN INCREASE IN THE NUMBER OF MONOCYTES IN THE BLOOD FOLLOWING SUBCUTANEOUS ADMINISTRATION OF YELLOW PHOSPHORUS IN OIL<sup>\*</sup>

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In recent years, a fairly large number of observations, both clinical and experimental, have been reported which indicate that there may be some obscure relationship between injury to the liver and the number of the circulating monocytes. The clinical observations include the changes in catarrhal jaundice<sup>1</sup> and those in accidental poisoning by tetrachlorethane<sup>2</sup>. The experimental observations that indicated this relationship of liver and monocyte were those of Holt<sup>3</sup> and of Huffman, Lawrence and Jones<sup>4</sup>. Holt observed that the ligation of a bile duct in the rabbit produced a marked and relatively well sustained increase in the number of monocytes, while Huffman, Lawrence and Jones injected sterile, macerated liver from normal rabbits into rabbits intraperitoneally and found a marked rise in the number of monocytes following this procedure.

In all these conditions, the one factor in common was the presence of injured liver tissue—if one can assume that in catarrhal jaundice the liver is actually injured. In consideration of this fact, namely, that the number of the monocytes in the circulating blood is increased in several conditions in which there is present injured hepatic tissue, the importance of further study of degeneration of the liver seemed indicated. In considering what type of degeneration of the liver to study, it seemed wise

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<sup>\*</sup> Submitted for publication, Dec 10 1928

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1 Jones, C M, and Minot, G R. Infectious (Catarrhal) Jaundice. An Attempt to Establish a Clinical Entity, Observations on the Excretion and Retention of the Bile Pigments, and on the Blood, Boston M & S J **189** 531, 1923. Thewlis, Ethel, and Middleton, W S. The Leucocytic Picture in Catarrhal Jaundice (Cholangitis), Am J M Sc **169** 59, 1925.

2 Minot, G R, and Smith, L W. The Blood in Tetrachlorethane Poisoning, Arch Int Med **28** 687 (Dec) 1921.

3 Holt, R B. Effect on White Blood Cells in Rabbit of Ligation of Common Bile Duct, Proc Soc Exper Biol & Med **24** 974, 1927.

4 Huffman, M M, Lawrence, J S, and Jones, Edgar. The Effect on the White Blood Cells Produced by Intraperitoneal Injection of Whole Liver, Arch Path, this issue, p 804.

to begin with that produced by the use of yellow phosphorus—the reason being that the degeneration produced by phosphorus is gradual and is characterized especially by a periportal distribution of the earliest changes. The literature bearing on this point is discussed elsewhere<sup>5</sup>

#### EXPERIMENTAL METHOD

This report is based on the results obtained in nineteen guinea-pigs. Thirteen of these animals received subcutaneous injections of phosphorus, and six were given phosphorus by mouth. Those receiving phosphorus subcutaneously received the injections at intervals of from three to five days, the individual dosage in the great majority of the cases being 0.5 mg. Five of these animals received a few injections of 1 mg. each. The smallest total dosage was 3.5 mg., the largest 5.5 mg. of phosphorus. The preparation used was made by Hynson, Westcott and Dunning from a stock solution of yellow phosphorus in almond oil. This stock solution contained 1 per cent of yellow phosphorus. Ten cubic centimeters of this solution was mixed with 90 cc. of olive oil, thus making 1 cc. of the final mixture equivalent to 1 mg. of yellow phosphorus.

Total and differential counts of the white cells were made daily for several days preceding and throughout the period of the injections of phosphorus. The supravital method was used in making all the differential counts.

Three of the six animals given phosphorus by mouth were given daily dosages of 1 mg. for from six to seven days, one was given 2 mg. daily for six days, and the remaining two were given 1 mg. every other day for six days, and then, after an interval of three days, a dose of 1 mg.

Complete autopsies were made on all the animals of both series, except guinea-pigs 38, 39, 40 and 41, which were used for further investigation and were in good condition at the time that the blood studies were discontinued.

An examination of the liver for fat (by staining frozen sections with scharlach r) was made in each case. Guinea-pigs 13, 14, 19, 22, 27, 28, 29, 30 and 31 showed evidence of phosphorus poisoning in the liver. Guinea-pigs 11, 18 and 24 showed questionable signs of phosphorus poisoning in the liver. Guinea-pigs 12, 24 and 26 did not reveal any fatty changes in the liver. Guinea-pig 13 had pneumonia. There was questionable pneumonia in guinea-pig 14. Guinea-pig 22 showed hemorrhage in the suprarenal glands. Guinea-pigs 13, 14, 22 and 27 died. The rest of the animals were killed.

In brief, these experiments resulted in the observation that in the early stages of phosphorus poisoning there is a marked increase in the number of monocytes in the circulating blood.

#### RESULTS

The animals that received subcutaneous injections of yellow phosphorus are divided into three groups, according to whether they showed a definite response in the blood, a questionable or equivocal response or no response following the injection of phosphorus. Group 1 consists of six guinea-pigs all of which showed definite changes in the number of circulating white cells following the injection of phosphorus. In each instance, the striking observation was an appreciable rise in the number

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<sup>5</sup> Lawrence, J. S., and Huffman, M. M. Fatty Changes in the Kupffer Cells of the Liver of the Guinea-Pig in Phosphorus Poisoning, *Arch. Path.*, this issue, p. 809.

of monocytes The highest value found was in guinea-pig 11 after the third injection of phosphorus The absolute number of monocytes at this time was 4,544, which was an increase of 4,002, or 738.4 per cent, over the average value of 542 found before the injection The lowest maximal monocyte value for any animal in this series was 2,225, in

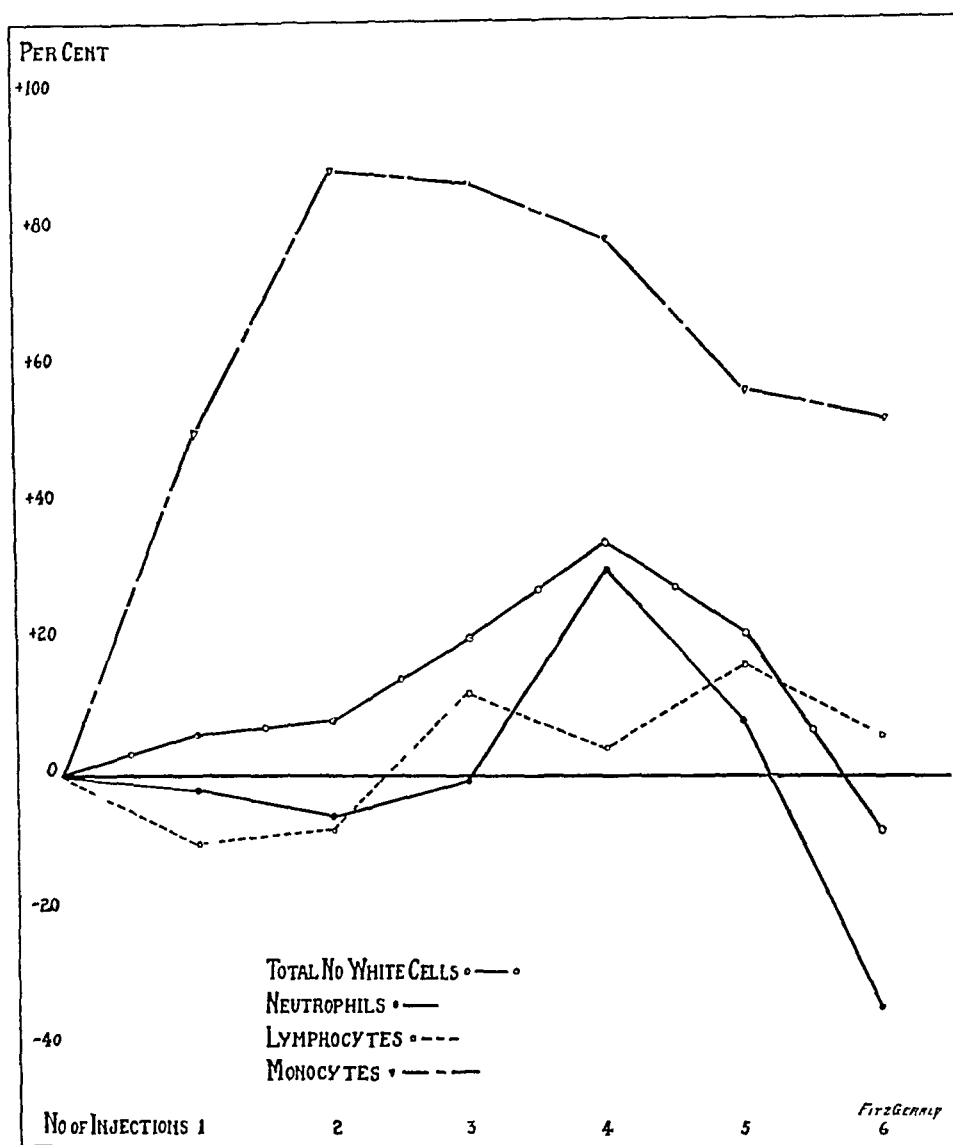


Chart 1—Average percentage variations in the blood counts of animals in group 1, following repeated injections of phosphorus

guinea-pig 41, after the fourth injection of phosphorus This was an increase of 1,332, or 149.2 per cent, over the value of 893 found before the injection

This monocytic response was greatest after the second and the third injections of phosphorus (chart 1) The maximal average percentage increase (87.9 per cent) in this experiment occurred after the second

injection Changes of note did not occur in the total number of white cells, or in the absolute number of neutrophils or lymphocytes The low peak reached by the curve of the total white cell counts and the curve of the neutrophil counts occurred considerably after the peak had been reached by the monocytes Table 1 represents the average values in a typical animal (guinea-pig 40)

Group 2 includes three animals that showed an equivalent response to the subcutaneous injections of phosphorus The number of the monocytes tended to run a level course, and in only one instance (guinea-pig 25) did the number show any appreciable increase In this case

TABLE 1—*Effect of Injection of Yellow Phosphorus on the Blood Counts in Guinea-Pig 40*

Time of Count	Average Number of White Cells per Cu Mm	Average Number of Neutrophils per Cu Mm	Average Number of Lymphocytes per Cu Mm	Average Number of Monocytes per Cu Mm
Before injections of phosphorus	8,640	7,008	2,320	971
After first injection	7,563	3,636	1,980	1,535
After second injection	9,017	4,680	1,909	1,740
After third injection	9,050	4,252	2,198	1,720
After fourth injection	9,725	4,512	2,549	1,818
After fifth injection	9,275	4,727	2,162	1,530
After sixth injection	7,250	2,791	2,249	1,486

TABLE 2—*Average Blood Counts in Animals Given Phosphorus by Mouth*

Guinea Pig	Total per Cu Mm		Neutrophils per Cu Mm		Lymphocytes per Cu Mm		Monocytes per Cu Mm	
	Before	After	Before	After	Before	After	Before	After
22	6,784	8,000	5,110	4,024	1,539	2,523	868	876
27	8,760	15,843	4,999	9,876	2,535	3,437	1,037	2,298
28	18,400	17,533	10,872	11,888	3,191	3,534	2,252	2,034
29	14,675	10,900	4,861	6,017	6,981	2,960	1,882	1,671
30	6,950	9,083	2,619	3,692	3,315	3,631	705	825
31	10,583	10,850	3,938	5,718	4,620	3,227	811	1,063
Average	11,024	12,035	5,400	6,903	3,700	3,219	1,259	1,461
Average difference in per cent		+9.2		+27.8		-13.0		+16.0

the increase was associated with an increase in the number of neutrophils In general, the number of neutrophils and that of lymphocytes did not show any appreciable change from the normal Chart 2 shows the average percentage changes in the blood counts of the animals in this group following injections of phosphorus

Group 3 consists of four animals that did not show any changes in the curves of the white cell counts These animals were treated in the same way as those of groups 1 and 2, but they failed to respond

The six animals given phosphorus by mouth did not exhibit the same response as those given phosphorus subcutaneously Four of these animals did not show any variations in the blood counts beyond normal limits The remaining two animals showed some changes in the curves One of these animals, guinea-pig 27, showed a marked terminal increase



in the number of monocytes associated with a rather marked leukocytosis. The maximal number of monocytes in this case was 5,615, and the total number of white cells at this time was 31,200. The second animal showing an increase in monocytes was no 31. The maximal value for monocytes in this animal was 2,184, but the average value after the

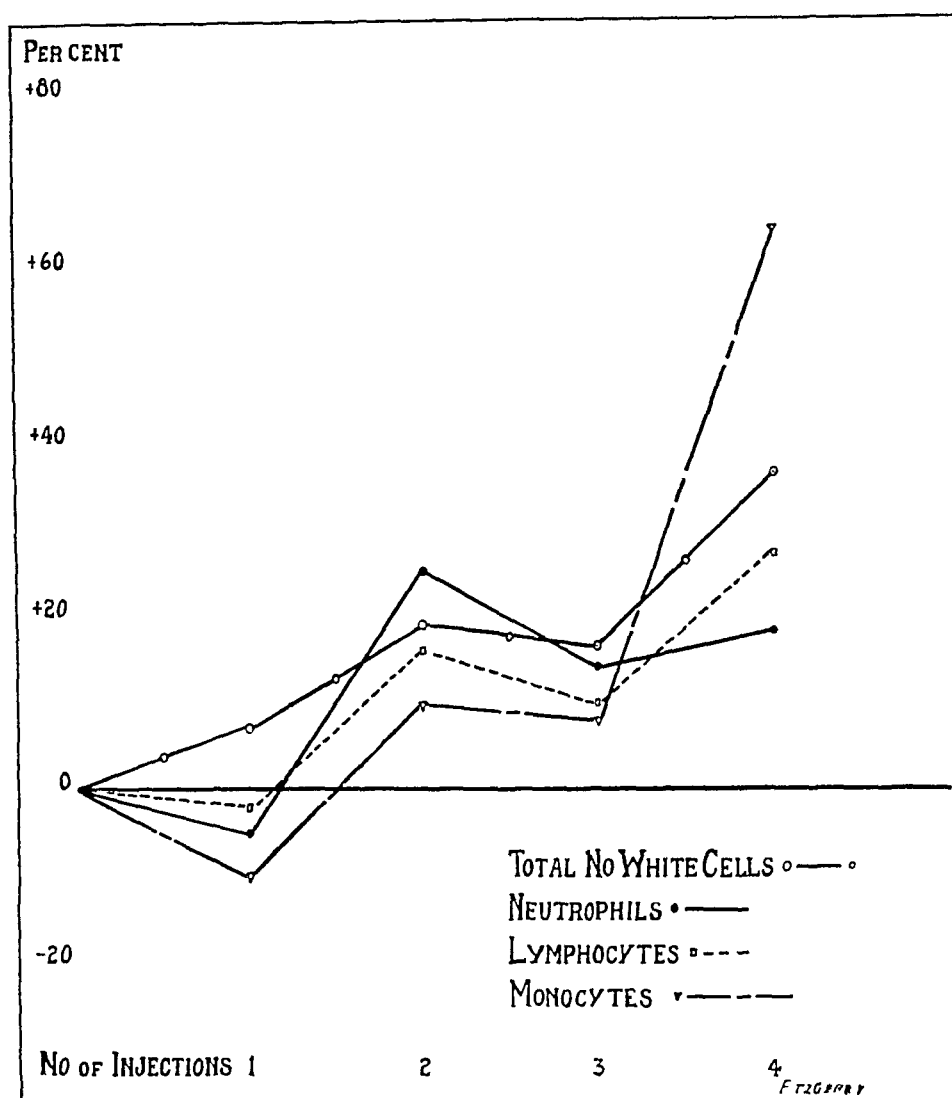


Chart 2—Average percentage variations in the blood counts of animals in group 2 following repeated injections of phosphorus

injection of phosphorus was only 1,063. The other white cells did not show any variation beyond the normal in this group of animals.

In addition to the aforementioned animals treated with phosphorus, two guinea-pigs (nos 124 and 125) were treated with repeated subcutaneous injections of 0.5 cc of olive oil and two (nos 126 and 127) with repeated subcutaneous injections of 0.5 cc of almond oil. The two guinea-pigs given olive oil showed absolutely no increase in

the number of monocytes in the blood stream Those given almond oil did not present so level a monocytic curve, but the variation was within the normal limits The highest value for monocytes in either of these animals was 1,627 after the injections against 1,118 prior to the injections This high value was present on only one occasion, the curve soon returning to a value below 1,000 per cubic millimeter

#### COMMENT

An increase in the number of circulating monocytes was found in the guinea-pigs of this series with sufficient regularity, following the subcutaneous injection of phosphorus, to indicate a definite relationship between the monocytic increase and the injections of phosphorus This suggests several possibilities

1 Was the increase in the number of circulating monocytes due to the phosphorus per se, or was it due to the olive oil or to the almond oil? That almond oil and olive oil alone were not responsible was indicated by the control experiments in which these substances were used without phosphorus In these control experiments, changes were not found in the white cell counts On the other hand, that phosphorus, as such, was not the only factor is indicated by the failure to get a similar response in the animals given phosphorus by mouth

2 Were the variations in the blood counts due directly to changes in the liver? Such a conclusion is not borne out by the pathologic observations Table 1 shows that there was a marked response of the monocytes in guinea-pigs 11 and 12, whereas the pathologic changes in these two animals did not give conclusive evidence of phosphorus poisoning in the liver, the observations in guinea-pig 12 being entirely negative in this regard The failure to demonstrate changes in the liver by examination of sections stained for fat, however, does not eliminate the possibility of changes being present It is possible that variations in structure and function that cannot be detected by this method may be present

3 Can the blood picture be explained by a general effect on the animal organism of some substance or substances produced by the action of phosphorus on the tissues? This seems a possibility, but we did not have any direct evidence in its favor

4 Are the monocytes in the blood stream derived from the tissues at the site of the injection, and, if so, is there a sufficient reaction quantitatively to account for the number of monocytes in the circulating blood? Sufficient evidence to answer this definitely has not yet been accumulated, as is indicated in the discussion on the tissues published elsewhere <sup>6</sup>

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6 Lawrence, J S , Tompkins, Edna H, and Cunningham R S The Production of Monocytes and Epithelioid Cells in Subcutaneous Tissue by Injection of Various Irritants, *Proc Soc Exper Biol & Med* 26 331, 1929

The effect of pneumonia on the blood counts of guinea-pig 13 is of interest, the greatest average increase in the number of monocytes in this animal occurred after the first injection of phosphorus and at a period when pneumonia was probably not present. On the other hand, the question of pneumonia cannot be entirely discarded, for it has been shown that there is an increase in the number of monocytes during the period of resolution.<sup>7</sup>

An analysis of the variations in the total number of white cells and in the absolute number of neutrophils and lymphocytes fails to reveal any indications of abnormality. This points definitely to an effect confined entirely to the monocytes.

The increase in the number of monocytes is as constant and as great as in tuberculosis. The question naturally arises whether there is, etiologically, any relationship between the monocytosis of tuberculosis and that following the administration of phosphorus. Of course, it is well known that there is an appreciable amount of phosphorus in the tubercle bacillus. And recently Sabin and Doan<sup>8</sup> showed that the phosphatide fraction of the tubercle bacillus is a potent stimulus to the production of monocytes. Obviously, it is possible that the two reactions have both phosphorus and fat in common, but whether the relationship can be carried any further is not apparent at present.

#### CONCLUSION

Subcutaneous injections of yellow phosphorus cause a marked increase in the number of the circulating monocytes.

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7 Hickling, R. A. The Monocytes in Pneumonia. A Clinical and Hematologic Study, *Arch. Int. Med.* **40** 594 (Nov.) 1927.

8 Sabin, Florence R., and Doan, C. A. The Biological Reactions in Rabbits to the Protein and Phosphatide Fractions from the Chemical Analysis of Human Tubercle Bacilli, *J. Exper. Med.* **46** 645, 1927.

# THE ORIGIN AND FATE OF SICKLE-SHAPED RED BLOOD CELLS \*

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Sickle-shaped red blood corpuscles are found so constantly in certain chronic anemias,<sup>1</sup> in unexplained fevers<sup>2</sup> and in sickle cell anemia,<sup>3</sup> and the prevailing views as to their method of origin and ultimate fate are so conflicting that it is important to elucidate the mechanism by which these cells assume their abnormal shape

Though Hayem<sup>1</sup> had long since drawn attention to these peculiarly shaped cells, it remained for the Sergent brothers<sup>2</sup> to describe them in detail as the "corps en demi-lune" Furthermore, they demonstrated<sup>4</sup> that these cells are not artefacts, as was maintained by Hayem and by Nicolle and Comte<sup>5</sup> Laveran,<sup>2</sup> in the discussion of the observations of the Sergents, expressed the view that the cellular defect is due to the departure of a parasite Others<sup>6</sup> maintained that the cells are produced by an altered osmotic condition of the cell membrane Still another conception is that the surface tension of the cell and serum is altered or that the phenomenon of adsorption occurs<sup>7</sup> Many believe that it is merely a mechanical distortion<sup>8</sup> Langeron<sup>9</sup> produced sickle cells in animals by injecting them with massive doses of lead Hahn

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\* From the New Rochelle Hospital

1 Hayem, Georges Du sang et de ses alterations anatomiques, 1889, Paris, G Masson (Masson et Cie), p 336

2 Sergent, E, and Sergent, É Sur des corps particuliers du sang des paludeens, *Compt rend Soc de biol* **58** 51, 1905

3 Herrick, J B Peculiar Elongated and Sickle Shaped Red Blood Corpuscles in a Case of Severe Anemia, *Arch Int Med* **6** 517 (Nov) 1910

4 Sergent, E, and Sergent, É Sur les corps en anneau et en demi-lune du sang des paludeens, *Compt rend Soc de biol* **59** 252, 1905, *Études épidémiologiques et prophylactiques du paludisme*, *Ann de l'inst Pasteur* **20** 245, 1906

5 Nicolle, C, and Comte, C Sur la signification des corps en anneau décrits par MM Sergent dans le sang des paludeens, *Compt rend Soc de biol* **58** 760, 1905

6 Leede, W N Gigantozyten bei Malaria, *Mitt a d Hamburg Staatskrankenanstalten* **13** 1, 1912

7 Josephs, H W Sickle Cell Anemia, *Bull Johns Hopkins Hosp* **40** 77, 1927

8 Brumpt, E Globules geants ou "corps en demi-lune" du paludisme, *Bull Soc path exot* **1** 201, 1908

9 Langeron, M Hematies en demi-lune dans le sang du rat et du cobaye, *Compt rend Soc de biol* **70** 434, 1911

and his co-workers<sup>10</sup> thought that asphyxia and anoxemia are causal factors. Many have named the spleen as the seat of the trouble.<sup>11</sup> Cooley and Lee<sup>12</sup> thought that the red blood cells possess a peculiar vulnerability to some hemolytic agent. Emmel<sup>13</sup> suggested that the manner in which these blood cells are transformed may be due to an abnormal activity of the same factors that cause the original erythrocyte to change to the biconcave disk.<sup>14</sup> That the anomaly is a congenital<sup>15</sup> or an anatomic defect<sup>16</sup> is supported by the reports of its occurrence in families.<sup>17</sup>

The variety of opinions as to the origin of sickle cells is due to the difficulty in seeing their change from the normal to the abnormal shape.<sup>18</sup> While it may be possible to establish certain criteria for the change by experimental modification, it seems that the mechanism of the alteration can be ascertained only by a detailed microscopic study of single cells.

#### MATERIAL AND METHODS

During the past year, fresh blood smears were made as a matter of routine for all negroes on admission to the hospital. A minute drop of the patient's blood was obtained on a cover slip. This was inverted over a glass slide. The rim of the cover slip was sealed with petrolatum or Canada balsam. Only smears that showed red blood cells singly, just touching, but not overlapping, or in rouleaux, were accepted for further study. Such smears can be secured by having the glassware scrupulously clean, the patient's finger free from grease and the size of the drop of blood just large enough to give a very thin spread. Though there were many failures, results were usually obtained by using new glassware, copious quantities of ether and alcohol and infinite patience. There were 213 colored patients in the series, twelve of whom showed sickle-shaped blood cells in peripheral and venous blood. Smears from these twelve cases were further studied by placing

10 Hahn, E. V., and Gillespie, E. B. Sickle Cell Anemia. Report of a Case Greatly Improved by Splenectomy, *Experimental Study of Sickle Cell Formation*, *Arch Int Med* **39** 233 (Feb.) 1927. Hahn, E. V. Sickle Cell (Depranocytic) Anemia, *Am J M Sc* **175** 206, 1928.

11 Dreyfoos. Sickle Cell Anemia, *Arch Pediat* **43** 436, 1926.

12 Cooley, T. B., and Lee, P. The Sickle Cell Phenomenon, *Am J Dis Child* **32** 334 (Sept.) 1926.

13 Emmel, V. E. A Study of the Erythrocyte in a Case of Severe Anemia with Elongated and Sickle Shaped Red Blood Corpuscles, *Arch Int Med* **20** 586 (Oct.) 1927.

14 Castana, V. I gigantocite e le anemia semilunari, *Pediatrics* **33** 431, 1925.

15 Dresbach, M. Elliptical Human Red Corpuscles, *Science* **19** 469, 1904, **21** 473, 1905.

16 Bishop, F. W. Elliptical Human Erythrocytes, *Arch Int Med* **14** 388 (Sept.) 1914.

17 Sydenstricker, V. P. Further Observations on Sickle Cell Anemia, *J A M A* **83** 12 (July 5) 1924.

18 Cook, J. E., and Meyer, J. Severe Anemia with Remarkable Elongated and Sickle Shaped Red Blood Cells and Chronic Leg Ulcer, *Arch Int Med* **16** 644 (Oct.) 1915.

the slide beneath the high power and oil immersion objectives of the microscope, fixing the slide in such a manner that it could not be moved and making camera lucida and free hand drawings of the changes going on in selected cells of a particular field every fifteen minutes. Simultaneous studies were conducted with the blood at room temperature, 0 C, and 37.5 C. It was thus possible to ascertain when and how the cells changed their shape, as well as the percentage of cells that remained normal after a given period.

### THE ORIGIN OF SICKLE CELLS

That the appearance of sickle-shaped red blood cells is subject to considerable variation has been repeatedly observed<sup>19</sup>. Some of the factors that seem to determine these differences are the clinical condition of the patient, the degree of anemia and the temperature of the

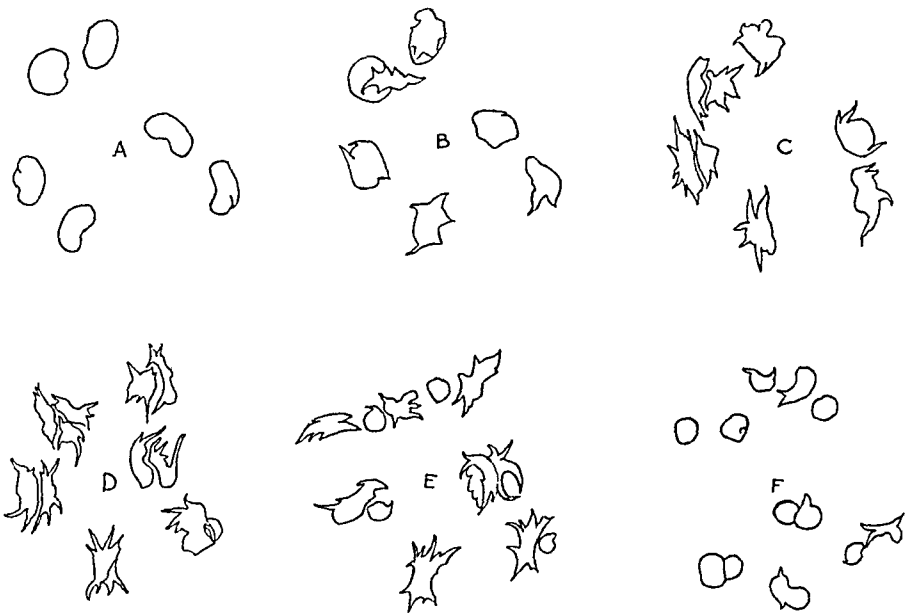


Fig 1—Camera lucida and free hand sketches of successive stages in the changing of red cells to sickle shape. A represents the cells as they appear immediately after their withdrawal from the blood stream, B, one hour later, C, two hours later, D, four hours later, E, twenty-four hours later, and F, seventy-two hours later.

blood *in vivo* and *in vitro*. While an increase in temperature hastened the phenomenon, a decrease retarded and in many cases actually inhibited it. Occasionally, sickle cells could be found in a smear immediately following the removal of the corpuscle from the blood stream (fig 1 A). Usually, one hour elapsed before the initial changes could be recorded. These consisted in the protrusion of short and long processes from the surface of the cell (fig 1 B). In some cells, the processes assumed the proportions of pseudopodia, in others, they appeared as mere con-

19 Anderson, H. B. Sickle Cell Anemia, *Am J M Sc* **171** 641, 1926

strictions in the cell membrane. There was a continual protrusion and retraction of these processes. The speed with which this sometimes occurred was startling. Kite<sup>20</sup> observed that a long process in the normal red blood corpuscles of man could be retracted in less than a second. With this continual and rapid rearrangement, it was not surprising to find that in the course of the second hour many of the cells had assumed an abnormal shape. In the majority of instances, especially in the so-called latent cases of sickle cell anemia, the projection of processes with consequent flattening and elongation of the corpuscle resulted in the production of sickle-shaped red blood cells.

In addition, some of these cells actually divided into two unequal parts (fig 1 C). A few of the daughter cells proceeded to subdivide (fig 1 D). All the divisions were indirect and the plan of the segmentation varied considerably. Jolly,<sup>21</sup> following the division of the red blood cells in young tritons for fifteen days in vitro, found that pressure determined the plan of segmentation, but did not initiate or inhibit division. On the other hand, Krehl and Marchand<sup>22</sup> quoted the experiences of Schultze, Rollet and Ranvier, who brought about division of red blood cells into microcytes and poikilocytes in vitro by pressure on the cover glass or by gently heating the fresh preparation. In repeating such experiments, it was found that while in preparations of normal blood one could easily cause the disintegration of the red blood cells by pressing on the coverslip, it was not possible to do so in cases that eventually showed sickle-shaped cells. The cells from these patients showed a rubber-like resilience and, though pressure could distort their shapes considerably, the cells did not disintegrate, and, when the pressure was removed, the cells returned to their characteristic form. Pressure on cells that had already assumed the sickle shape, but which did not show any tendency to divide, also brought out the pliability of these cells, yet again they did not break up or return to their original spherical shape. It seems, therefore, that the phenomenon observed was an actual division of the red blood cell and not a mechanical artefact.

Those corpuscles that become sickle-shaped before or after dividing are in reality embryonic cells. For in the same field as that in which the division or the projection of processes is being observed, one may find certain cells extruding their nuclei (fig 2 B). Following the extrusion of the nucleus, the mother cell at first cup-shaped, rapidly becomes sickle-shaped. The method by which the change to the sickle

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<sup>20</sup> Kite, G. L. Some Structural Transformations of the Blood Cells of Vertebrates, *J. Infect. Dis.* **15** 319, 1914.

<sup>21</sup> Jolly, J. Recherches experimentales sur la division indirecte des globules rouges, *Arch. d'anat. micr.* **6** 455, 1903.

<sup>22</sup> Krehl, L., and Marchand, F. Handbuch der allgemeinen Pathologie, Leipzig, S. Huzel, 1908, vol. 1, p. 51.

shape occurs is by the extension of pseudopodia in the manner mentioned. Furthermore, as has been shown repeatedly, stained smears in active cases of sickle cell anemia contain large numbers of normoblasts<sup>23</sup>. That immature red blood cells may have the power of independent multiplication was long ago demonstrated by Howell<sup>24</sup>. Phylogenetically, direct amitotic division has been demonstrated in the cold-blooded animals,<sup>25</sup> while Mencl<sup>26</sup> illustrated the division of nucleated red blood cells in *Scorpaena*.

The evidence shows that sickle-shaped red blood cells are formed from embryonic normoblasts that have prematurely entered the general circulation, these cells then continue their maturation by dividing or extruding their nuclei, the resultant cells still immature are then unable to assume the biconcave disk form, but continue as ameboid shapes until an alteration is effected that gives them a favorable nidus.

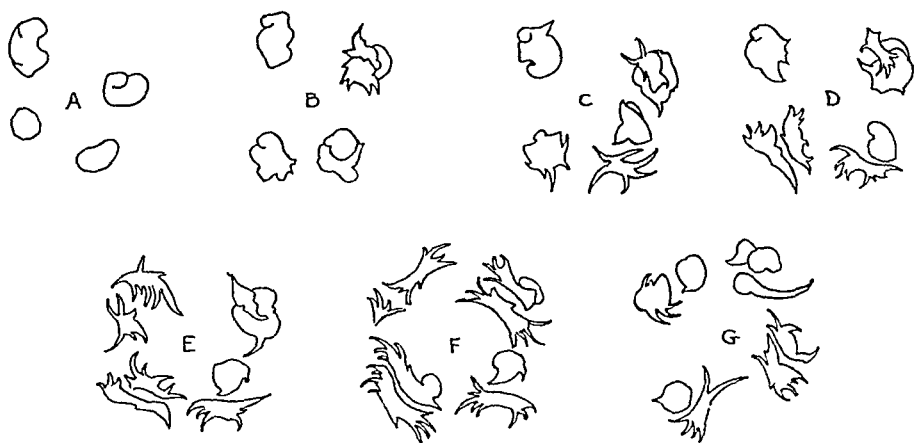


Fig 2—Camera lucida and free hand sketches of successive stages in the transformation of red blood cells into sickle-shaped cells. A represents the cells as they appear fifteen minutes after their removal from the blood stream, B, one and a half hours after, C, one and three quarters after, D, two hours after, E, three hours after, F, twelve hours after, and G, nine days after.

#### THE FATE OF SICKLE CELLS

While it seems plausible that the sickle cells may form as a result of a disturbance in erythropoiesis, it is difficult to understand why some corpuscles assume the form of the biconcave disk (fig 1 F), while

23 Huck, J. G. Sickle Cell Anemia, Bull. Johns Hopkins Hosp. **23** 335, 1923.

24 Howell, W. H. The Life History of the Formed Elements of the Blood, Especially the Red Blood Corpuscles, J. Morphol. **4** 57, 1890.

25 Zillberberg, L. A. On the Direct Amitotic Division of Red Corpuscles of Cold Blooded Animals, Russk. Arch. Patol. Klin. Med. i Bakteriol. **11** 545, 1901.

26 Mencl, E. Direkte Teilung von roten Blutkörperchen bei *Scorpaena*, Anat. Anz. **37** 539, 1910.



others retain their bizarre shape (fig 2 G) Though Oliver<sup>27</sup> demonstrated the separation of spinous and elongated processes from normal erythrocytes in man, such a phenomenon is not found in sickle cells In a long continued study of such corpuscles in the hermetically sealed wet smears, one is struck not only by the great variations in shape from hour to hour but also by the individual differences between supposedly sister cells The latter may be accounted for by the angle or plane through which the cell is viewed Jordan<sup>28</sup> showed that the red blood corpuscle is normally a circular biconcave disk but appears to be cup shape when seen obliquely, and dumb-bell shape when seen in profile<sup>29</sup> While a few of the cells of abnormal shape were seen to retract their processes immediately and become round, the great majority continued to project new but blunter pseudopodia (fig 1 E) This continued for many hours until finally all the processes were retracted and one found only circular, cup-shaped or peculiarly indented cells (fig 1 F)

Under certain conditions, especially in those patients showing sickle cells without symptoms, the change from the sickle shape to the original form did not occur After the initial alteration in shape, the cells had not the faculty to change further, they retained their bizarre appearance for an indefinite time (fig 2 G)

The speed of the phenomenon of reversion varied with the temperature at which the blood was kept The changes depicted in figures 1 and 2 were those that occurred at room temperatures of from 18 to 24 C When the smears were kept in the incubator at body temperature (37.5 C), these changes were completed within twenty-four hours. Later changes consisted in the rapid fragmentation of the red blood corpuscles, until one observed numerous microcytes mingled with occasional cells of normal size Many of the microcytes were phagocytosed by the white corpuscles Further fragmentation was sometimes prevented by removing the blood from the incubator and placing it in the refrigerator at 0 C When freshly drawn blood from patients, who normally showed sickle-shaped cells was placed immediately at 0 C the development of sickle cells rarely occurred But if the blood was allowed to remain at room temperature for an hour or two and then was placed in the refrigerator, one could demonstrate the presence of sickle-shaped cells in the preparations for as long as three months In other words, refrigeration acted as a fixative, while incubation at body temperature caused the destruction of the red cells by fragmentation Rous

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27 Oliver, W. W. The Crenation and Flagellation of Human Erythrocytes, *Science* **40** 645, 1914

28 Jordan, H. E. The Shape of the Human Red Blood Corpuscles, *Proc. Soc. Exper. Biol. & Med.* **12** 167, 1914

29 Radasch, H. E. Observations upon the Form of the Red Blood Corpuscles of Man, *Am. J. M. Sc.* **131** 837, 1906

and Robertson<sup>30</sup> found that erythrocytes of normal and anemic rabbits were destroyed by fragmentation

#### CONCLUSIONS

The change to the sickle shape observed in red cells is a phase in a profound disturbance of the formation of red blood cells. Embryonic red blood cells and normoblasts enter the systemic circulation. These cells proceed to divide or extrude their nuclei. The resultant cells project pseudopodia and assume bizarre shapes. Heat (body temperature) hastens the change, cold (0 C) inhibits and may actually prevent it. After varying periods, some of the abnormally shaped red cells retract their pseudopodia and return to the parent form, others retain their bizarre shapes permanently. Refrigeration (0 C) prevents the return of the cell from sickle shape to the form of the biconcave disk. Sickle cells kept at body temperature eventually disintegrate by fragmentation.

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30 Rous, P., and Robertson, O. H. Normal Fate of Erythrocytes. I. The Findings in Healthy Animals, *J. Exper. Med.* **25** 651, 1917. Normal Fate of Erythrocytes. II. Blood Destruction in Plethoric Animals and in Animals with a Simple Anemia, *ibid.* **25** 665, 1917.

# ANAPHYLAXIS IN THE WHITE RAT AS INFLUENCED BY DIET<sup>\*</sup>

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It has, in general, been impossible to produce anaphylactic shock in the white rat by the usual procedures employed in such animals as the guinea-pig and the rabbit. Among the early studies on anaphylaxis in this animal, the experiments of Trommsdorff<sup>1</sup> are among the most extensive. He was entirely unable to obtain symptoms of shock in the rat. His results are in agreement with those of Uhlenhuth,<sup>2</sup> Rosenau and Anderson<sup>3</sup> and Galli-Valerio<sup>4</sup>. The latter, however, used *Mus rattus* and *Mus decumanus*. On the other hand, Arthus<sup>5</sup> reported that he was able to produce anaphylaxis in white rats. He promised that details of the procedure would be published in the future, but so far as can be determined they have not appeared. More recently, Novy and De Kruif,<sup>6</sup> as well as Longcope,<sup>7</sup> have reaffirmed the refractoriness of white rats to anaphylactic shock. Opie<sup>8</sup> was unable to reproduce the Arthus phenomenon in these animals.

In contradistinction to this considerable accumulation of negative results, Parker and Parker<sup>9</sup> were able consistently to produce

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<sup>\*</sup> Submitted for publication, Jan. 4, 1929.

<sup>\*</sup> From the Department of Bacteriology, College of Physicians and Surgeons, Columbia University.

1 Trommsdorff, R. Ueber biologische Eiweissdifferenzierung bei Ratten und Mäusen, *Archiv für Gesamte Anatomie* **32**: 560, 1909.

2 Uhlenhuth and Weidanz. Ausführung des biologischen Eiweiss Differenzierungsverfahrens, Jena, Gustav Fischer, 1909, *Centralblatt für Bakteriologie* (pt. 1, ref., suppl.) **47**: 68, 1910.

3 Rosenau, M. J., and Anderson, G. F. A Study of the Cause of Sudden Death Following the Injection of Horse Serum, *Hygienic Laboratory Bulletin*, no. 29, U. S. Pub. Health Service, Washington, D. C., 1906.

4 Galli-Valerio, B. Peut-on utiliser *Mus rattus* pour le diagnostic des taches de sang par le procédé l'anaphylaxie, *Zeitschrift für Immunitätsforschung und experimentelle Therapie* **5**: 659, 1910.

5 Arthus, M. M. Injections répétées de sérum de cheval chez le lapin, *Comptes rendus Société de biologie* **55**: 817, 1903.

6 Novy, F. G., and De Kruif, P. H. IX. Specific Anaphylactic Shock, *J. Infect. Dis.* **20**: 776, 1917.

7 Longcope, W. T. Sensitization and Anaphylactic Shock, *J. Exper. Med.* **36**: 627, 1922.

8 Opie, E. L. Inflammatory Reactions of the Immune Animal to Antigen and Its Relation to Antibodies, *J. Immunol.* **9**: 231, 1924.

9 Parker, J. T., and Parker, F. Anaphylaxis in the White Rat, *J. Med. Research* **44**: 263, 1924.

anaphylactic shock in the white rat. Three of twenty-eight animals sensitized to sheep serum died on reinjection of the antigen, nine had severe shock and all but one showed definite symptoms. Ebert,<sup>10</sup> repeating their technic, was unable to obtain their results. Only one of twenty-nine animals showed definite symptoms as described by Parker and Parker.

Two recent workers have succeeded in producing shock in white rats under special conditions. Flashman,<sup>11</sup> while unable to produce shock in normal rats, was successful in those from which the suprarenal glands had been removed. Wedgewood and Grant<sup>12</sup> reported that while animals on a normal diet were immune to anaphylactic shock, rats on a diet deficient in vitamin B could be killed on the second injection of the antigen. The observations of Sartori<sup>13</sup> and of Sereni<sup>14</sup> are related to this problem of the effect of diet on anaphylaxis. These investigators reported that guinea-pigs on a diet deficient in vitamins are more acutely sensitized, and thus after a shorter incubation period, than the control animals.

As there was reason to believe from contemporary reports from the animal house that the rats of Parker and Parker were maintained chiefly on a diet of bread and water, which is distinctly deficient in all the vitamins including vitamin B, which Wedgewood and Grant have identified as necessary to the rat's resistance to anaphylactic shock, we planned a series of experiments to test the effect of a dietary of bread and water on anaphylaxis in the rat.

#### EXPERIMENTS

*Anaphylaxis in Animals on Complete Diet*—Using the same technic as reported by Parker and Parker, we endeavored to sensitize the white rat with the following antigens: sheep serum, rabbit serum, rabbit red cells, pigeon red cells and suspensions of killed streptococci. The animals either failed to show any signs of shock on reinjection of the antigen or exhibited only transitory and rather indefinite signs, such as slight ruffling of the hair, a temporary increase in the depth of respiration and occasionally some decrease in muscle tone, as indicated by

10 Ebert, M. K. Zur Frage des Zustandekommens des anaphylaktischen Shocks bei weissen Ratten, *Ztschr f Immunitätsforsch u exper Therap* **51** 79, 1927.

11 Flashman, D. H. The Effect of Suprarenalectomy on Active Anaphylactic Shock in the White Rat, *J Infect Dis* **38** 461, 1926.

12 Wedgewood, P. E., and Grant, A. H. The Chemical Basis of Immunity. I. The Influence of Vitamin B upon Anaphylaxis, *M Bull Univ of Cincinnati* **2** 172, 1924.

13 Sartori. Anafilassi ed avitaminosi, *Pathologica* **17** 160, 1925.

14 Sereni, E. Anafilassi ed avitaminosi, *Boll d Soc ital di biol sper* **2** 254, 1927.

flabbiness of the animal when handled. Gross and microscopic changes were not found at autopsy.

Fourteen animals were used in this experiment, and the dose of the antigen that caused shock was injected as many as twenty-four times, some of the animals being given injections repeatedly. The diet of these rats consisted of bread and water, oats, carrots, cheese and lettuce.

*Anaphylaxis in Animals on a Diet of Bread and Water*—Thirty-eight animals, twenty-four of which had been sired by the same father and raised in the laboratory, were divided into two groups. Sixteen were maintained on a diet of bread and milk, oats and carrots to which cabbage or lettuce was frequently added. The rest were put on a diet of white bread and water, after they had attained a weight of 100 Gm or more. They were maintained on this diet at least two weeks before the sensitizing dose of antigen was given. On this diet, the animals appeared to be normal, but gained weight only slowly. All the animals were kept in the back of the room, where they were not exposed to any direct sunlight.

All the animals were prepared by a single intraperitoneal injection of sheep serum. The dose was usually 1 cc, although an occasional large animal was given as much as 2 cc. The shocking dose of sheep serum was also 1 cc, given nine or more days later, either intravenously or intracardially. The animals were usually kept for repeated shocking doses at similar time intervals. They were ultimately examined post mortem and the tissues prepared for histologic examination, except for a few animals still under observation.

Many of the animals were bled, from 0.5 to 1 cc being withdrawn from the heart under ether anesthesia, previous to the administration of the shocking dose of antigen. The serum from this blood was titrated for its precipitin, and in a few cases for its precipitinogen content.

The original toxicity of the antigen was tested by the intravenous injection of 2 cc or more into animals of both groups. Symptoms were not elicited. Serum from the same sheep was used throughout the experiments. Specificity of the anaphylactic shock and desensitization were also demonstrated.

The results are given in detail in tables 1 and 2. Animals on a diet of white bread and water were subject regularly to symptoms of anaphylactic shock in a manner analogous to that described by Parker and Parker. There is little to add to their description or to that of Flashman, who obtained similar results in rats from which the suprarenal glands had been removed. In about three minutes, the animal's respirations become labored and the abdomen, at the points of insertion of the diaphragm, is retracted markedly with each inspiration. Inspiration often becomes audible and always sounds harsh through the stethoscope. There is frequently a blood-tinged discharge from the nose. The eyes are exophthalmic and the ears, in the severer cases, become pale. The animal flattens itself on its belly and sometimes actually sprawls out on its entire ventral surface with all four legs extended. It may become intensely cyanotic.

TABLE 1—*The Active Sensitization to Sheep Serum of Animals on a Diet of White Bread and Water*

Rat	Date	Weight, Gm	Days on Diet	Days Since Last Injection	Amount Injected, Cc	Place of Injection	Degree of Shock*	Gross Pathologic Changes*	Titer of Pre-cipitin	Minimal Temperature, F
1	June 16	132	17		1	Peritoneal cavity				
	June 25	135	26	9	1	Heart	++			95
	July 9	140	40	14	1	Tail vein	—			102.7
	July 20	145	51	11	1	Tail vein	0			102
	July 28		59	8	1	Heart	0	0		100.4
2	Sept 22	218	53		2	Peritoneal cavity				
	Nov 4		86	33	2	Foot vein	++			97.5
5	June 16	152	17		1	Peritoneal cavity				
	June 25	154	26	9	1	Heart	+++	+++		95.5
6	June 14	199	15		1	Peritoneal cavity				
	June 23	183	24	9	1	Heart	++			96.4
	July 3	182	34	10	1	Vein	++			96.9
	July 13	180	44	10	1	Vein	++	+		97.1
7	June 14	125	15		1	Peritoneal cavity				
	June 23	106	24	9	1	Heart	++			96
10	May 25	119	17		1	Peritoneal cavity				
	July 4		27	10	1	Vein	+++	±		95.1
11	May 25	127	17		1	Peritoneal cavity				
	July 5	126	28	11	1	Heart	+			99.7
	July 14		37	9	0.6	Subcutaneous				
	July 24	103	47	10	1	Heart	++	+		96.6
12	May 25	134	17		1	Peritoneal cavity				
	July 5	133	28	11	1	Heart	++	0		96.3
13	July 29	129	33		1	Peritoneal cavity				
	Aug 7	145	42	9	1	Tail vein	++			96.4
	Aug 17		52	10	1	Heart	+++	++	1.40	97
14	Aug 4	110	30		1	Peritoneal cavity				
	Aug 14	113	40	10	1	Vein	+++			97.2
	Aug 27		53	13	1	Heart	+++	++	1.20	95
15	Aug 20	137	55		1	Peritoneal cavity				
	Aug 30		65	10	1	Heart	++	+		96
16	Aug 14	100	49		1	Peritoneal cavity				
	Aug 23		58	9	1	Heart	++		1.10	96
	Sept 7		73	15	1	Heart	+++	++++	1.40	92
17	Oct 2		96		2	Peritoneal cavity				
	Nov 4		129	33	1	Foot vein	++			96.9
18	Aug 1	103	27		1	Peritoneal cavity				
	Aug 11	109	37	10	1	Heart	+		1.10	93.3
	Aug 22		48	11	1	Heart	++		1.10	96
	Sept 5		62	14	1	Foot vein	+++	++	1.40	94.7
19	Aug 4	118	30		1	Peritoneal cavity				
	Aug 14		40	10	1	Vein	++		1.20	96.5
	Aug 17		43	3	1	Heart		Hemorrhage from heart	1.40	
28	Aug 14	118	40		1	Peritoneal cavity				
	Aug 23		49	9	1	Heart	Ditto	+	1.80	96
29	Sept 18	122	75		1	Peritoneal cavity				
	Sept 27		84	9	1	Vein	++		0	95.5
	Oct 17		104	20	1	Heart	++			96.5
	Oct 26	145	113	9	1	Foot vein	+++			93.9
	Nov 16		134	21	0.5	Vein				
30					0.5	Subcutaneous	+-		1.160	98
	Aug 21	100	47		1	Peritoneal cavity				
	Aug 30		56	9	1	Heart	+		1.10	98
	Sept 10	110	67	11	1	Heart	++		1.40	96.6
	Sept 20	115	77	10	1	Foot vein	+-		1.20	97.2
	Oct 25	135	106	29	1	Foot vein	+			100.4
	Nov 14		125	19	1	Foot vein	+-		1.10	98.6
31	Sept 19	125	76		1	Peritoneal cavity				
	Sept 29		85	9	1	Foot vein	+			98
	Oct 26	130	113	28	1	Foot vein	+			99
	Nov 9		127	14	1	Vein	++		1.1280	94.2

\* Under the column headed "Degree of Shock" + indicates change in respiration rate and ruffling of hair without prostration or lowering of temperature ++ indicates the same and, in addition, lowering of the temperature by at least 3 degrees Fahrenheit, and slight prostration, +++ indicates the same as ++ with marked prostration ++++ indicates the same as +++ followed by death Similar marks in the column headed "Gross Pathologic Changes" give a rough indication of the extent of the petechial hemorrhages

TABLE 1—*The Active Sensitization to Sheep Serum of Animals on a Diet of White Bread and Water—Continued*

Rat	Date	Weight, Gm	Days on Diet	Days Since Last Injection	Amount Injected, Cc	Place of Injection	Degree of Shock	Gross Pathologic Changes	Titer of Pre-cipitin	Minimal Temperature, F
32	Aug 2 Aug 11	98 112	24 33	9	1 1 2	Peritoneal cavity Heart	+++	++		96
33	Aug 1 Aug 11	92 92	21 31	10	1 1	Peritoneal cavity Heart	++++	++++		96
36	July 28 Aug 6 Aug 22 Sept 5  Sept 18  Sept 27 Oct 26 Nov 9	93  102     130	17 26 42 56  69  78 107 120	9 9 16 14  13  9 29 13	1 1 1 0 3 0 4 0 3 0 5 1 1 1	Peritoneal cavity Heart Heart Vein Subcutaneous Vein Peritoneal cavity Vein Vein Foot vein	+ + + ++ ++ ++ ++ ++ +		97 8 96 1 10 1 40  1 40  1 40 1 20	93 1 93 4 98 1 95

TABLE 2—*Active Sensitization to Sheep Serum of Animals on Diet of Oats, Bread, Milk and Carrots*

Rat	Date	Weight, Gm	Days Since Last Injection	Amount Injected, Cc	Place of Injection	Degree of Shock*	Gross Pathologic Changes*	Titer of Pre-cipitin	Minimal Temperature, F
Pn 4	June 25 July 9			1 9 1	Tail vein Tail vein				
4	June 18 June 27	150 162 153	14 9	1 1	Peritoneal cavity Tail vein	+	0		101 2 100 8
8	June 12 June 21	120	9	1 2	Peritoneal cavity Heart	0	0		
9	June 12 June 21	129	9	0 9	Peritoneal cavity Tail vein	+	0		
21	July 29 Aug 17 Aug 27	120 148	19 10	1 1 1	Peritoneal cavity Peritoneal cavity Heart	0 ++	+	1 5 1 10	95 5
23	Aug 14 Aug 23	158	9	1 2	Peritoneal cavity Vein	0		0	100 6
25	Aug 20 Aug 30 Sept 10 Sept 20 Oct 29 Nov 14	148 165 165	10 10 10 39 16	1 1 1 1 0 7 0 3	Peritoneal cavity Foot vein Tail vein Foot vein Peritoneal cavity Foot vein Subcutaneous	+ 0 0 0 +?		0 1 40 1 15 1 40	99 8 99 3 98 8 98 7
26	Aug 21 Aug 30 Sept 11 Sept 20  Oct 29 Nov 14	160 200 215	9 11 9  39 16	1 1 0 7 0 3 1 0 7 0 3	Peritoneal cavity Heart Peritoneal cavity Tail vein Subcutaneous Foot vein Tail vein Subcutaneous	+ 0 0 0 +?		0 1 10 1 40 1 20	99 93 2 100
27	Sept 18 Sept 27 Oct 29 Nov 14	225	9 32 16	1 7 1 1 0 5 1	Peritoneal cavity Foot vein Foot vein Tail vein Subcutaneous	0 0 0		1 5 1 40	100
34	Sept 19 Sept 29 Oct 26 Nov 9	140 130	10 27 14	1 1 1	Peritoneal cavity Foot vein Foot vein Vein	++ + +		1 40 1 80	95 1 99 4 100
Im I	Sept 10 Sept 20	310	10	2 2	Vein Tail vein	0			99 6

\* For meaning of signs, see table 1

In the severe cases, general flaccidity develops. The animal is limp, and all reflexes disappear. The respirations become shallow and rapid. Tonic and clonic convulsions and opisthotonos occur intermittently. One animal excreted a bloody urine, and several animals had a bloody discharge from the rectum.

As will be seen from table 1, among the animals on bread and water, one animal died, eight showed marked signs of shock at one time or another, and all but one exhibited distinct signs of shock. The drop in temperature was a pronounced and constant feature of the shock, amounting to from 3 to 10 F.

In table 2, detailed information is given concerning the eleven animals on a complete diet. These animals constitute a control group for the series described in table 1. Two animals showed distinct signs of shock with a drop in temperature at one time, five showed slight, questionable reactions to the antigen, without a drop in temperature, and four did not show any reaction. Five other animals were lost as the result of hemorrhage from the heart.

#### PATHOLOGY

With two exceptions, those animals on a diet of bread and water that were examined post mortem following anaphylactic shock showed a uniform pathologic picture, varying only in extent and intensity. Petechial hemorrhages in the viscera were the outstanding feature, as already reported by Parker and Parker.<sup>9</sup> The mesenteric lymph nodes were the first organs to exhibit hemorrhage, while the liver and the gastro-intestinal tract were the next most common sites. Peyer's patches were only occasionally involved. There was often free blood in the stomach and small intestine. In the severer cases, minute hemorrhages in the pancreas, kidneys and lungs could be demonstrated. These varied from pin point, almost submacroscopic size, to a size about 2 mm in diameter. The lungs, at the stage at which these animals were examined post mortem, were not emphysematous.

One of the animals on a full diet which were examined post mortem showed two small hemorrhages in two of the mesenteric lymph nodes, the others were, in the gross, normal.

In view of the fact that Flashman produced anaphylaxis in rats from which the suprarenal glands had been removed, it is interesting to note the difference in the size of these glands in the two series of animals. The suprarenal glands taken after autopsy were measured in the three dimensions. By this rather crude method, the suprarenal glands of the animals on bread and water were ascertained to be approximately one half the size of the suprarenal glands of the animals on a complete diet, while the average body weights of the animals in these two series differed by only 17 Gm, the one series averaging 141 Gm, the other 124 Gm. This difference in size could not be



explained on the basis of sex. Female rats were about equally distributed in both groups.

Rat 1, which failed to show an anaphylactic response two times out of four, was the only animal of the series on bread and water that had suprarenal glands comparable in size with those of the control group, while the smallest suprarenal glands were found in rat 33, female, which died of shock.

These observations suggest that the two sets of animals, those on complete diet and those on bread and water, may not differ in their fundamental response to the foreign protein, sheep serum, but may differ in some protective mechanism supplied by the secretions of the suprarenal glands.

A more complete gross study and a histologic study of these animals will be reported at a later time.

TABLE 3—*Precipitinogen Content of the Serum of White Rats Sensitized to Sheep Serum*

Rat	Total Amount of Sheep Serum Injected, Cc	Amount of Last Injection, Cc	Days Since Last Injection	Highest Dilution Giving Ring
27	18	18	9	1:160
34	1	1	10	1:80
	3	1	14	1:40*
35	1	1	10	1:160
	3	1	14	1:12*
Im I	19	2	6	1:640
29†	1	1	9	1:320
31†	1	1	10	1:160
	3	1	14	0
36†	7	1	14	1:20*

\* Rings faint and rather inconclusive.

† The last three animals belong to the series on a diet of bread and water.

#### PRECIPITIN AND PRECIPITINOGEN CONTENT OF THE SERUMS

The precipitin and precipitinogen content of the rats' serums was determined by means of the ring test in small tubes made from glass tubing with an inside diameter of 3 mm. The readings were taken after one and a half hours' incubation at 37 C. Appropriate control tubes with sodium chloride solution and with serum from normal rats, both on a complete and on a bread and water diet, were also prepared. It was found advisable in determining the titer of the precipitin to dilute the rats' serums 1:2 because of the frequency of a ring when physiologic solution of sodium chloride was layered over undiluted rat serum. The numbers given in the table under the heading "Titer of Precipitin" represent the highest dilutions of sheep serum antigen to give a ring. The titer is actually somewhat higher, as the rat serum had been diluted as mentioned. With the exception of rat 31 from the series on bread and water, the serum of which showed a titer of precipitin far in excess of the titers of precipitin of the serums of the other animals, the two

series did not show any striking difference in the titers of the precipitin of their serums. Formation of precipitin in the rat is therefore not marked, as has already been reported by Longcope<sup>7</sup> and by Spain and Grove<sup>15</sup>.

The precipitinogen content of the serum was determined in only a few rats by means of a strong, undiluted rabbit antishoop serum, which, when tested with sheep serum, gave a titer of 1:25,000 by the ring method described. Table 3 details the results. The sheep serum had almost disappeared from the rats' circulation at the end of fourteen days, which agrees with Longcope's observations. Evidence of a difference between the two series of animals in the precipitinogen content of their serums was not presented in these few experiments.

#### SUMMARY

Pronounced symptoms of anaphylactic shock cannot be produced in white rats on a diet of oats, bread, milk and greens.

Symptoms of anaphylactic shock can be constantly produced in white rats on a diet of white bread and water.

The gross lesions of anaphylaxis in the white rat are small petechial hemorrhages into various viscera, notably the mesenteric lymph nodes, the liver, the gastro-intestinal tract, the kidney, the pancreas and the lung.

The suprarenal glands of rats on a diet of bread and water are considerably smaller than those of animals on a complete diet.

So far as investigated, the titer of the precipitin and the titer of the precipitinogen content of the serum of sensitized rats on a diet of bread and water do not differ significantly from the corresponding titers of the serum of sensitized animals on a diet of oats, greens, bread and milk.

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15 Spain, W. C., and Grove, E. F. Studies in Specific Hypersensitiveness XII. A Study in Rat Precipitin, *J. Immunol.* **10**: 433, 1925.

# Laboratory Methods and Technical Notes

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## A SIMPLE GLYCEROL WATER CRYSTAL VIOLET POTATO CYLINDER MEDIUM FOR DIAGNOSTIC CULTURES OF TUBERCLE BACILLI

H J CORPER, M D, AND NAO UYEI, PH D, DENVER

In previous communications,<sup>1</sup> results were reported which led to a new method for the isolation and cultivation of tubercle bacilli from contaminated tuberculous materials. In a later report,<sup>2</sup> it was demonstrated that the new method is superior to Petroff's method of isolation and equals in efficiency the method that employs inoculation of guinea-pigs for the detection of the presence of tubercle bacilli in urines, sputums, tissues and other contaminated materials, and in many respects surpasses the latter method for practical diagnostic purposes.<sup>3</sup>

Further observations on the urine in doubtful cases and experiments with pure tubercle bacilli in salt solution have confirmed the previous observations demonstrating the efficiency of the new culture method as compared with the method that employs inoculation of guinea-pigs.

In one of the earlier reports,<sup>2</sup> it was pointed out that crystal violet, when incorporated in a medium of mashed potato and agar, exerted a deleterious effect on the growth of the tubercle bacilli. This was further confirmed on more extensive study. Therefore mediums made of mashed potato and agar cannot be recommended for use in the isolation of tubercle bacilli. When, however, it is desired to take advantage of the growth-promoting properties of potato incorporated in a solid medium similar to an agar medium for growing pure transplants of tubercle bacilli, the following simple medium is advised, with the omission of the crystal violet and broth.

Mashed autoclaved potato	25 per cent by weight
Glycerol	25 per cent by weight
Agar-agar	15 per cent by weight
Distilled water	71 per cent by weight

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\* Submitted for publication, Dec 17, 1928

\* From the Research Department, National Jewish Hospital

1 Corper, H J, and Uyei, Nao. The Isolation of Tubercle Bacilli from Contaminated Tuberculosis Materials, *Am Rev Tuberc* **16** 299, 1927, The Cultivation of Tubercle Bacilli. An Improved Method for Isolation from Tuberculous Materials, *J Lab & Clin Med* **13** 469, 1928

2 Corper, H J, and Uyei, Nao. Further Observations with a New Method for Cultivating Tubercle Bacilli. A Comparison with Guinea-Pig Inoculation and Petroff's Method, *J Lab & Clin Med* **14** 393, 1929

3 Corper, H J. The Certified Diagnosis of Tuberculosis, *J A M A* **91** 371 (Aug 11) 1928

This nutrient medium cannot, however, replace the crystal violet potato cylinder medium for the isolation of tubercle bacilli from contaminated tuberculous materials

Note was made in our earlier reports that broth added to the potato cylinder medium used in the new culture method, played a more or less indifferent rôle in promoting the growth of the tubercle bacilli on this medium. The possibility of obviating the use of broth in the potato medium was therefore suggested. In order to test this point more carefully before the omission of broth from the medium was recommended, potato cylinder crystal violet mediums were prepared containing varying amounts of pure glycerol in aqueous solution, and their efficiency for use in the growing of tubercle bacilli was compared with the medium previously recommended, which contained crystal violet

TABLE 1—*Crystal Violet Potato Cylinders in Glycerol Water Compared with Crystal Violet Potato Cylinders in Glycerol Broth as Mediums for the Growth of Tubercle Bacilli*

Amount of Glycerol Solution in Which Crystal Violet Potato Cylinder* Was Contained	Amount of Virulent Human Tubercle Bacilli in Milligrams per Cubic Centimeter in Suspension Used for Seeding Culture Tubes with Growth Resulting		
	1 Mg per Cc	0.0001 Mg per Cc	0.000,001 Mg per Cc
5% glycerol broth	Luxuriant	Marked	Marked
5% glycerol water	Luxuriant	Marked	Marked
4% glycerol water	Marked	Marked	Marked
3% glycerol water	Marked	Appreciable	Appreciable
2% glycerol water	Marked	Appreciable	Not appreciable
1% glycerol water	Appreciable	Appreciable	Not appreciable

\* The potato cylinders were prepared by immersing the clearest cylinders in a freshly mixed solution of 0.0015 per cent crystal violet in 1 per cent sodium carbonate

potato cylinders in 1.5 cc of 5 per cent glycerol broth. The results of this test are recorded in table 1.

In order further to test the value of the glycerol water in replacing the glycerol broth in the preparation of the crystal violet potato cylinder medium used for detecting tubercle bacilli in tuberculous materials, comparative studies were made in which from 1 to 7 per cent glycerol water was tested, positive sputums being used as test material and 5 per cent glycerol broth crystal violet potato cylinder medium as control. The sputums were prepared for culture by treatment with an equal volume of 6 per cent sulphuric acid, as recommended in the previous reports. The results of this study in the isolation of tubercle bacilli from sputums are recorded in table 2.

It is to be noted from an examination of the data recorded in tables 1 and 2 that glycerol water, containing glycerol in strengths of from 4 to 7 per cent, added to the crystal violet potato cylinders yielded growths of tubercle bacilli equally well and with as few contaminations as did the 5 per cent glycerol broth crystal violet potato cylinder

medium Similar results were obtained when other tuberculous materials were used for the test and when bovine tubercle bacilli were used

Since the use of glycerol water in place of glycerol broth markedly simplifies the preparation of the medium, the sulphuric acid potato method for the isolation and detection of tubercle bacilli consists essentially in the following procedures

One cubic centimeter of suspected material is beaten to a homogeneous pulp and introduced into a sterile centrifuge tube of 15 cc capacity with 1 cc of 6 per cent sulphuric acid (containing 17 cc of 96 per cent [specific gravity, 1.84] sulphuric acid in 500 cc of distilled water) and mixed After incubation at 37 C for thirty minutes, the contents of the tube are mixed with about 10 cc of sterile

TABLE 2—Comparison of Glycerol Water Crystal Violet Potato Cylinder Medium with Glycerol Broth Crystal Violet Potato Cylinder Medium for Cultivating Tubercle Bacilli from Sputum

Amount of Glycerol Solution in Which Crystal Violet Potato Cylinder† Was Contained	Results Obtained, in Percentage of Tubes Planted*	
	Contaminations, per Cent	Isolations, per Cent
5% glycerol broth (control)	4	93
1% glycerol water	1	99
0% glycerol water	0	99
5% glycerol water	3	96
4% glycerol water	3	97
3% glycerol water	5	83
2% glycerol water	3	89
1% glycerol water	3	84

\* In this table are recorded the results of the isolation of tubercle bacilli from fifteen specimens of sputums that were positive in stained smears examined under the microscope, five tubes of medium being used for the testing of each specimen of sputum, making a total of seventy five tubes from which the percentage of the contaminations and the isolations in the respective columns were figured

† The percentage of glycerol recorded is the amount contained in the 15 cc of the solution placed in the culture tube in which the potato cylinder rested

0.9 per cent sodium chloride solution and centrifuged The residue, after the supernatant fluid has been decanted, is seeded on the surface of the glycerol water crystal violet potato cylinder medium, the culture tube being capped with tin foil after the cotton plug has been lightly impregnated with hot paraffin to prevent drying out of the medium The medium is prepared by placing 15 cc of 6 per cent aqueous solution of glycerol (made with pure tap water or distilled water) in a sterile culture tube, 6 inches by  $\frac{3}{4}$  inch (15.24 by 1.9 cm) in size, in which has been inserted the crystal violet potato cylinder, about 3 inches (7.6 cm) long and  $\frac{5}{8}$  inch (1.59 cm) in diameter The latter is made by soaking a clean potato cylinder halved longitudinally, in a freshly mixed 0.0015 per cent standard crystal violet in 1 per cent sodium carbonate solution (prepared from the pure anhydrous salt) The entire medium is sterilized in an autoclave at 15 pounds (6.8 Kg) pressure for thirty minutes Excessive or prolonged heating of the medium during sterilization is to be avoided The culture tubes should be incubated in the dark with due precaution being taken to avoid drying of the medium or contamination A luxuriant growth should occur on this medium within from two to six weeks, but if the culture is negative, the tubes should not be discarded for diagnostic purposes until after three months' observation at incubator temperature

## SUMMARY

In the sulphuric acid potato culture method for the diagnosis of tuberculosis, 6 per cent glycerol water can be used to replace the 5 per cent glycerol broth previously recommended for the preparation of the crystal violet potato cylinder medium. This simplifies the preparation of the culture medium used in this new diagnostic method.

Human and bovine tubercle bacilli grow with equal facility when present in small numbers in tuberculous materials on the crystal violet potato cylinder medium with glycerol water in the absence of broth.

# General Review

## HUMAN PALEOPATHOLOGY

WITH SOME ORIGINAL OBSERVATIONS ON SYMMETRICAL  
OSTEOPOROSIS OF THE SKULL<sup>1</sup>

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BUFFALO

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\* From the University of Buffalo, School of Medicine

The word paleopathology was coined by Ruffer<sup>1</sup> as a name for the science of disease in persons of ancient times. The pursuit of any branch of knowledge for its own sake does not need justification, however, it is manifest that paleopathology may be of use in helping to explain diseases of the present time. It may, for instance, throw light on the origin of some of the infections. Again, the contrast between the diet and habits of primitive men and those of civilized men opens a field for study of diseases of the teeth that may yield results of practical value to men of the present day.

The monographs, papers and abstracts from which this review has been compiled have been found, for the most part, in journals of archeology, ethnology and anthropology, and in the reports of surveys, of museums and of learned societies in various parts of the world. As such sources of information are not easily accessible to pathologists, it is hoped that the review may be useful to them. Obviously, some valuable material may have been overlooked, furthermore, new material is coming to light almost daily.

#### SOME CASES OF IDENTIFICATION

Precisely where, in point of time, the paleopathology of man begins and ends is not easy to define, nor is it a matter of great moment. The case of Admiral John Paul Jones, distinguished for his services to the American colonies during the war of the Revolution, may not belong to ancient history, but it is sufficiently outside the routine experience of pathologists to be worth recalling.

Jones was buried in Paris in 1792, the body being enclosed in a coffin of lead containing alcohol. In 1905, when his remains were removed for transportation to the United States, even the features of the face were found corresponding exactly with a bust made during his life. The identification by anthropologists was supplemented by an autopsy that seems to have given satisfactory results.<sup>2</sup>

The lungs, heart, liver, stomach, spleen and kidneys were in the main well preserved. A scar in the left lung was attributed to an attack of pneumonia that Jones was known to have had three years prior to his death and which was said by physicians in Paris a year later to have affected his left lung permanently. The striations of the cardiac muscle were visible. The spleen was large and firm. The liver was yellowish brown and somewhat contracted, the liver cells were not well preserved. Some of the vessels of the kidney were sclerotic and the

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1 Ruffer, M. A. *Path & Bact* **18** 149, 1913, *Paleopathology of Egypt*, Chicago, University of Chicago Press, 1921, p. 139.

2 Porter, Horace. *The Recovery of the Body of John Paul Jones*. *Century Magazine* **70** 948, 1905.



glomeruli were in part fibrous. Bacteria were demonstrated in the liver and the kidneys. A diagnosis of "interstitial nephritis" was made, and it was stated that the results of the autopsy were consistent with the history, the patient having had severe dropsy for a week or more before his death. The report on the histologic changes and its conclusions were confirmed by Cornil. The excellent preservation of this body for 113 years was doubtless due to the alcohol. The odor of alcohol was still evident in spite of a crack in the coffin.<sup>3</sup>

Another case in which the condition of the body assisted in its identification was that of Don Francisco Pizarro, whose remains were exhumed at Lima, Peru, in 1891, on the 350th anniversary of his death. Pizarro was known to have been assassinated, and the wounds found on the body, in particular one on the right side of the neck, corresponded with those described in the accounts of his tragic end. Apparently, embalming had not been done, but the muscles, tendons and vessels could be traced, and the right eye was recognizable. The face in general and the viscera were not well preserved.<sup>4</sup>

An interesting, if not entirely convincing, story is related by Furst<sup>5</sup> of an Icelandic tradition to the effect that King Olav Geirstadaalv, of the ninth century, was a tall man who died having a disease of the foot. A great mound said to have been built by this king yielded the skeleton of a tall man whose bones were deformed by "rheumatism," especially one foot and the left knee.

Among the many dramatic episodes brought to light in the study of Egyptian mummies is one of exceptional interest related by Elliott Smith.<sup>6</sup> An explorer of Egyptian antiquities had searched for the mummy of Queen Tiy, wife of the Pharaoh Amenophis III, of the eighteenth dynasty, and he thought he had found it. Other Egyptologists maintained that the archeologic evidence proved that the mummy was that of the heretic King Akhenaton (Amenophis IV). The bones were submitted to Smith as those of the queen. To his surprise, he was forced to the conclusion that the skeleton was that of a young man and not that of an old lady. However, the condition of the epiphyses pointed to an age of about 23 years, certainly not more than 30 years, if

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3 It would be interesting to know whether or not this incident inspired an amusing, if somewhat irreverent, song, popular among college students a few years ago.

4 McGee, W. J. Remains of Don Francisco Pizarro, *Am Anthropol* **7** 1, 1894.

5 Furst, C. M. *Nar de doda vittna*, Stockholm, Svenska Teknologforeningens (Tissell's) forlag, 1920, abstr., *Anthropologie* **33** 605, 1923.

6 Smith, G. E. *Cambridge Univ Med Soc Mag*, 1926, p. 32. Smith, G. E., and Dawson, W. R. *Egyptian Mummies*, London, George Allen & Unwin, 1924, *The Broadway, Westminster Hosp Gaz* **4** 25, 1928.

the owner of the skeleton was normal. The historical evidence indicated that the king was at least 30 years old and probably 36 when he died. It happened that a number of contemporary portraits of Akhenaton had come down to these times. His feminine appearance in these portraits had long been remarked. As his skull indicated a slight degree of hydrocephalus, and his lower jaw was somewhat overgrown, an additional sign of disease of the hypophysis, Smith<sup>6</sup> suggested that Akhenaton may have been a victim of dystrophia adiposogenitalis, or Froelich's syndrome, which leads to a delayed union of the epiphyses.

From such examples, occurring within historic times, which could be multiplied, human paleopathology may be extended to a time 50,000 or more years earlier when evidences of disease in the bones and teeth of the Neandertal man of the latter part of the glacial period were encountered. The bodies of Eskimos, encased in ice and several centuries old, have been discovered in Alaska, and long-haired mammoths have been found in the frozen mud of northern Siberia, the carcasses of which had been well preserved by the cold for many thousands of years. Though it may seem fantastic, it is not impossible that some pathologist may yet have the thrilling experience of making an autopsy on the frozen or desiccated body of a Neandertal man.

#### CHRONOLOGY

For the chronology, one must rely on archeologists. Their methods are essentially those of geologists. When strata lie one above another, objects found in the lowest levels should be the oldest. However, there are possibilities of error that have led to many controversies. Burial may introduce a skeleton into a level lower than that to which it belongs (intrusive burial). A stratum formed under water may contain objects that have washed in from an older stratum. An Indian may have picked up the bone of a mastodon, as any one might do, if such a bone were found buried with the Indian, it might lead to the erroneous conclusion that this Indian and this mastodon were contemporaries. Strata formed by recent rains and floods may falsely seem continuous with older strata. I myself extracted an intact beer bottle from gravel that I had supposed dated from the middle of the glacial period. Evidently, the amateur archeologist may easily make mistakes, while professional archeologists may sometimes hold diverse opinions.

Archeologists have projected chronology backward by many thousands of years. The end of the glacial period is the earliest date that can be stated approximately in years, and it may be placed at from 10,000 to 30,000 years ago. Some of the discrepancy in these figures may be explained when one recollects that the glacial period must have come to an end in such a region as the neighborhood of New York

much earlier than it did in such localities as Montreal, about 300 miles farther north. The glacial period has not yet come to an end in Greenland.<sup>7</sup> The early Egyptians may have had a neolithic culture when much of the Scandinavian peninsula was buried in ice.

It appears that in the glacial (or pleistocene) period there were several long intervals during which the ice receded and warm climates prevailed. Penck, of Munich, has recognized in Europe four glacial periods, named Gunz, Mindel, Riss and Wurm, the first being the oldest. They were separated by three interglacial periods, as the Riss-Wurm and so on. Estimates of the lapse of time required for the four glacial periods and the three interglacial periods vary from more than 100,000 to 1,000,000 years.

In North America, there are evidences that the ice sheet advanced and receded as in Europe, but it is not at present possible to coordinate the glacial periods and the interglacial periods of the two continents. It seems expedient to introduce these elementary facts and those that are given in the immediately ensuing paragraphs, since it will be necessary to refer repeatedly to the chronology adopted.<sup>8</sup>

As is well known, archeologists have designated stages in the development of human culture according to the use in them of iron or bronze or polished stone or rough stone. These stages may be arranged in a chronological table, omitting all but general headings, as follows:

Iron age, beginning about 1500 B. C. to 500 B. C.

Bronze age, beginning about 4000 B. C. to 1000 B. C.

Neolithic age, beginning about 10000 B. C.

Paleolithic age, including

The reindeer period, or period of cave artists, men of modern skeletal type,	} subdivided into Magdalenian, Solutrean and Aurignacian	} Latter part of the Wurm glaciation from 15,000 to 40,000 years ago
Neandertal or Mousterian race	} Earlier part of the Wurm glaciation and the Riss- Wurm interglacial period	

Iron and bronze were employed in southwestern Asia and in Egypt long before they were introduced into western Europe. The oldest objects of iron that I can learn of are some iron beads discovered by Flinders Petrie in a predynastic tomb in Egypt (i.e., of 3400 B. C. or earlier). The tomb of King Tut-ankh-amen (1400 B. C.) contained

<sup>7</sup> For a concise and readable account of the glacial period, I refer the reader to Coleman, A. P. *Ice Ages, Recent and Ancient*, New York, The Macmillan Company, 1926.

<sup>8</sup> There are many excellent works largely devoted to these subjects. MacCurdy, G. G. *Human Origins*, New York, D. Appleton & Company, 1924; Osborn, *Men of the Old Stone Age*, New York, Charles Scribner's Sons, 1918; Boule, *Les hommes fossiles*, Paris, Masson & Cie, 1923; Obermaier, *Fossil Man in Spain*, New York, Hispanic Society, 1924.

a fine dagger and other well made articles of iron<sup>9</sup> Bronze was the metal in use at the time of the Trojan war

During the bronze age, cremation was practiced in some parts of Europe so that human remains are largely lacking from those regions It is customary to refer objects found in Egypt to one of the numerous dynasties, the first of which, according to Breasted, had its beginning about 3400 B C

The most important event in the chronological table is the appearance of men of the modern skeletal type (including the so-called Cro-Magnon race) in the latter part of the Wurm glaciation

Still, going backward, one finds the transition from modern man to Neandertal man abrupt The number of skulls and even of fairly complete skeletons of Neandertal man is large enough to make his reconstruction possible He was short, stocky, powerful, bending at the knees, with his head protruding forward and showing a strong lower jaw and teeth, with chin receding or wanting, a large face, eye-sockets large, eyebrow ridges prominent, forehead receding and a foreshortenment rather far back His brain was of good size, and the convolutions were, in general, the same as those in modern man, but somewhat simpler The frontal bones were relatively less developed He was right-handed He used fire He buried his dead, which accounts for the considerable number of finds of skeletal remains He is the original caveman of fiction, the low-brow of modern slang A majority of anthropologists appears to believe that Neandertal man was a different species from modern man and that he became wholly extinct Hrdlička, of the United States National Museum, Washington, has ably defended the position that modern man is descended from Neandertal man, and that this development occurred in central Europe

The possibility that atavistic and now criminal tendencies inherited from Neandertal man may appear in individuals of the present offers an interesting field for speculation But it may be that a great injustice has been done Neandertal man, for all one knows, he may have had a mild and gentle disposition, while having a forbidding exterior

Although numerous stone implements have been found that belong to the middle or early parts of the glacial period, at present only two fragments of human remains are known to have come from those remote times the Heidelberg or Mauer jaw, which does not show any pathologic condition, and the incomplete Piltdown skull The latter is so thick as to have suggested that it came from a man with acromegaly<sup>10</sup> or from one with Paget's disease

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<sup>9</sup> Carter, Howard The Tomb of Tut-anekh-amen, New York, Doubleday, Doran & Company, 1927, vol 2, p 248 The examination of the body of King Tut-anekh-amen by Derry did not give results of importance to pathologists

<sup>10</sup> Adams, J G Medical Contributions to the Study of Evolution, New York, The Macmillan Company, 1918

Shattock<sup>11</sup> made a careful study of this famous skull from the point of view of the pathologist. While he excluded osteitis deformans, acromegaly and several other conditions as causes of the thickening, he seemed to think that it might have been due to rickets, and concluded that, at least, it may have been pathologic. I have had the opportunity to give the Piltdown skull a brief inspection, and was impressed with the fact that it was extremely thick, and that this thickness might be pathologic, but the nature of the material did not permit an exact diagnosis.

In America, it is exceedingly difficult to determine the age of native human remains. The Indians continued to use the implements of their own culture long after the white race came. In fact, in Mexico and in our own Southwest, one may any day see a woman grinding corn in a stone metate within a few yards of automobiles and railroads. The presence in a grave of glass beads or iron axes may prove that the burial was recent, but the absence of such articles does not prove that it was ancient. Superimposed strata containing evidences of different cultures, such as are common in Europe, are rather rare in America. Much progress in defining the sequence of cultures has been made in Peru, in Central America, in the Southwest of the United States and in Ohio, to mention some of the best known fields. Realizing the immense activity of American archeologists, one may look forward to a solution of many of the difficulties before long.

Whether or not there is reliable evidence for the existence of man in America during the glacial period is still, as it has been for many years, a matter of lively controversy. Anthropologists seem fairly agreed that the Indians constitute a well defined race, that their progenitors came from Asia by successive migrations and that their sojourn in America has been a long one. In a previous paper,<sup>12</sup> I suggested that the probable absence from America of most of the infections of worldwide distribution, prior to the time of the discovery, and the great susceptibility of the Indians to infections introduced from Europe are indications that the separation of the American race from the races of the Eurasian continent has been a long one.

#### MATERIALS

History contributes to paleopathology facts of the utmost importance, but in the present review only the material sources will be considered. The largest proportion of the facts of human paleopathology has come from the study of ancient bones and teeth. These are the only sources

<sup>11</sup> Shattock, S. G. Tr. XVIIIth Internat. Cong. Med., London, 1913. Sec. on Path., p. 3.

<sup>12</sup> Williams, H. U. Bull. Johns Hopkins Hosp. **20**: 339, 1909.

of evidence for the conditions of disease of the earlier periods of man's history

The bones of neolithic, late-paleolithic and Neandertal man which show signs of disease are preserved in museums scattered over western and central Europe. The publications in which they are described are scattered in like fashion. Egypt has furnished an enormous amount of material, which dates from the late prehistoric era down to early Christian times. Smith<sup>13</sup> has examined about 30,000 ancient Egyptian and Nubian bodies, while Wood-Jones<sup>13</sup> based his report on the examination of 6,000 bodies more than all the rest of the world has given to the science of disease in ancient man.

At the time of the enlargement of the great Assuan dam, near the border where ancient Egypt and Nubia met, it was recognized that the region to be flooded contained a vast quantity of priceless archeologic material. Fortunately for science, the study of the human remains was entrusted to Smith, who was assisted by Wood-Jones and Derry. Their labors were begun in 1907, and were completed in 1910, and their final report was given out in 1910. To appreciate the value of their labors, one must realize how time-consuming are the measurements of the skull and skeleton made by physical anthropologists, the personal discomforts attending field work in Nubia and the fact that some of the gentlemen named carried on, at the same time, their regular duties at the medical school in Cairo. The promptness with which their results were given to the world under these conditions and their thorough but concise analysis of that great mass of human remains challenge admiration. It is to be regretted that their reports<sup>13</sup> are not more easily accessible to the general student.

For facts concerning the paleopathology of Egypt, one is also indebted to the studies of Ruffer<sup>1</sup>. Besides these there are numerous less extensive articles on material from Egypt.

In America, one is fortunate in having brief notes on the bones of the North American Indians made early by a competent pathologist, Whitney<sup>14</sup> as well as the excellent paper of Landon<sup>15</sup>. The largest single source of South American Indian remains has been Peru, and

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13 Wood-Jones, F. General Pathology, Fractures and Dislocations, in Human Remains, Archeological Survey of Nubia, Report for 1907-1908, Cairo, 1910, vol. 2. Smith, G. E., Wood-Jones, F., Derry, D. E. Articles in Bull. Archeological Survey of Nubia, 1908-1910, nos. 1-6. Smith, G. E., and Dawson, W. R. Egyptian Mummies, London, George Allen & Unwin, 1924. The latter contains a good brief summary of the pathologic conditions encountered in Egyptian remains.

14 Whitney, W. F. Diseases of the Bones of North American Indians, Rep. Peabody Museum 3 433, 1884.

15 Landon, F. W. Madisonville (Ohio) Pre-Historic Cemetery, J. Cincinnati Soc. Nat. Hist. 4 247, 1881.

the most complete reports on the pathologic conditions shown in the bones are those of Hrdlička<sup>16</sup> and MacCurdy,<sup>17</sup> both reports furnished with beautiful illustrations. I am greatly indebted, also, to Moodie<sup>18</sup> for the facts that he has assembled, bearing on both continents. Within a few years, a large quantity of skeletal material of the Pueblo Indians has been excavated at Pecos, N. M., in the United States, by Kidder. The human remains will be the subject of a report by Hooton.<sup>19</sup> Unfortunately, it is not available for the purposes of this review. I had the opportunity of giving some of these bones a brief inspection and found that there are among them cases of symmetrical osteoporosis of the cranium, of fractures, of osteomyelitis, possibly some of tuberculosis, of probable osteomalacia and of thickening of various long bones that might have been produced by syphilis or by periostitis or by osteitis deformans. There are also among them cases of arthritis deformans. Much remains to be done in studying the pathologic conditions of the bones of Indians deposited in the great museums.

#### TECHNIC

Bones, when first unearthed, are sometimes so soft and fragile that it is desirable to endeavor to preserve them by infiltration with such materials as paraffin or shellac. Sections of bone and teeth may be made by grinding, the technic for which is described in textbooks of histology, so that it need not be repeated here. Sections may be made after bone has been decalcified by the usual methods. Even when a bone is hundreds of years old, it is best to fix it in formaldehyde before decalcification. Some old bones are infiltrated with so much calcium carbonate that decalcification must be done carefully on account of the evolution of carbon dioxide, which tears the tissue. Embedding in celloidin is usually recommended. If the amount of organic framework left is slight, decalcification may be performed after embedding the tissue in celloidin. In one case, I obtained usable sections by this method when decalcification before embedding had reduced the tissue to a formless jelly. A recent monograph from Aschoff's laboratory considers the preparation of ground sections of bone and their examination by transmitted, reflected and polarized light, with especial reference to the study of ancient specimens.<sup>20</sup>

16 Hrdlička, A. Pathology of the Ancient Peruvians, Smithsonian Coll **61** 57, 1914

17 MacCurdy, G. G. Human Skeletal Remains from the Highlands of Peru, Am J Phys Anthropol **6** 217, 1923

18 Moodie, R. L. Paleopathology, Urbana, Ill., University Illinois Press, 1923

19 Hooton, E. A., to be published by the Phillips Academy, Andover, Mass

20 Weber, Moritz. Schliffe von Rohrknochen und ihre Bedeutung für die Unterscheidung der Syphilis und Osteomyelitis von der Osteodystrophia fibrosa, sowie für die Untersuchung fraglich syphilitischer prähistorischer Knochen, Beitr z path Anat u z allg Path **78** 442, 1927

## OBSERVATIONS ON ANCIENT BONES

Erosion of bones by natural forces after death, including roots of plants and rodent animals, may produce results that simulate the effects of diseases destructive of bone. Elliott Smith<sup>21</sup> discussed errors of diagnosis in the case of certain ancient Egyptian bones that had been gnawed by a small beetle.

*Deformations*—Examples of arrested or defective development are not rarely observed in ancient bony remains, such as cleft palate, metopic suture and the presence of an interparietal bone. The latter is said to be frequent in native Peruvian skulls, and is often called the Inca bone. Deformity of the skull may be natural or artificial. Both kinds are widely distributed. The possible relation of asymmetry of the cranium to disease of the nervous system is discussed briefly by Raymond<sup>22</sup>.

Artificial deformation results from pressure on some portion of the head exerted during infancy. Such deformity may have been unintentional, and was common among many American Indians when the occiput of the baby constantly pressed on a resistant support. Intentional deformation of the skull has been practiced in many parts of the world and from early periods. A good brief account of it, with references to the literature, was given by Hrdlička,<sup>23</sup> who said the effects on the health of the subject were insignificant.

Large symmetrical depressions on the parietal bone, which have been attributed to senile atrophy or to congenital defect, and which are usually rare, were found by Smith<sup>24</sup> with great frequency in bodies from ancient Egypt, but only in remains from the upper classes of certain periods and of certain localities. One cemetery at the Pyramids yielded seventy examples. It was suggested that the depressions were produced by the wearing of heavy wigs.

Hydrocephalus was described by Derry<sup>25</sup> as occurring in an Egyptian (Roman Period) associated with atrophy of the bones of the left side, indicating hemiplegia. Another case of hydrocephalus in remains from a Merovingian cemetery at Weimar has been reported on by Pfeiffer<sup>26</sup>.

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21 Smith, G. E. *Lancet* **2** 521, 1908.

22 Raymond, Paul. *Les maladies de nos ancêtres de l'âge de la pierre*, Aesculape **2** 122, 1912.

23 Hrdlička, A. *Handbook of American Indians*, Washington, Bureau of American Ethnology, Bull. 30, pt. 1, 1907, p. 96.

24 Smith (footnote 6, first reference, p. 38).

25 Derry, D. E. *J. Anat. & Physiol.* **47** 436, 1913.

26 Pfeiffer, L. *Cor-Bld allg Aerzt v. Thuringen* **29** 426, 1900.



Smith<sup>27</sup> described talipes equinovarius in the mummy of Siptah (nineteenth dynasty, about 1410 B C) Dawson mentioned another reported by Murray as observed in a mummy of the twelfth dynasty Ruffer and Dawson copied a number of ancient Egyptian drawings of clubfoot in their articles on dwarfs and deformed persons<sup>28</sup>

Cretinism was diagnosed in connection with an Egyptian skull of the eighteenth dynasty by Seligmann,<sup>29</sup> who discussed the points of distinction from achondroplasia

*Rickets*—One is impressed with the small amount of evidence of rickets in the material from ancient Egypt Wood-Jones,<sup>13</sup> in 1908, found none in 6,000 bodies His statement was confirmed by Smith and Dawson<sup>6</sup> in 1924, after a much larger material was available Ruffer, in his article on dwarfs and other deformed persons in ancient Egypt, reproduced drawings of bow-legged persons who, he believed, must have had rickets Klebs<sup>30</sup> alluded to the "bow-legged god Bes and the rachitic child on amulets of the Saitic-Persian period (Berlin Museum von Oefele)" I have met with one reference to rachitic bones of northern Europe of the neolithic period, this was by Carl Furst,<sup>5</sup> who mentioned several cases in remains from Denmark and a probable case in remains from Norway There is little recorded evidence of rickets in the bones of ancient America Clay figures like hunchbacks were alluded to by Whitney,<sup>14</sup> the same author made no reference to rickets as having been seen in the bones examined by him Lehmann-Nitsche merely mentioned a few bones as rachitic in his report on arthritis deformans Hrdlička,<sup>23</sup> whose opportunities for the examination of the bones of American Indians have been enormous, said that "rachitis did not exist in the pre-Columbian Indian" It has been suggested that symmetrical osteoporosis of the cranium described in the following section is a condition allied to rickets

The condition known as osteitis fibrosa (von Recklinghausen) and that known as osteitis deformans (Paget), now considered by many German pathologists under one heading as osteodystrophia fibrosa, seems to have been almost ignored in the study of ancient osseous remains, further research on such material is needed

27 Smith (footnote 6, second reference), *The Royal Mummies*, Cairo, 1912 From the Service des Antiquites de l'Égypte, Catalogue Generale des Antiquites, Égyptienne J Musée de Caire, nos 61051-61100

28 Ruffer, M A On Dwarfs and Other Deformed Persons, *Bull Soc Archeol d'Alexandrie*, no 13, reprinted (footnote 1, second reference) Dawson, W R Dwarfs and Hunchbacks in Ancient Egypt, *Ann M History* 9 315, 1927

29 Seligmann, C G *Man* 12 17, 1912 An interesting outlook on cretinism is that of Finkheimer, Ernst Die kretinische Entartung nach anthropologischer Methode bearbeitet, Berlin, Julius Springer, 1919, abstr, *Arch f Anthropol*, 1923, vol 55

30 Klebs, Arnold *Bull Johns Hopkins Hosp* 17 214, 1917

Moodie<sup>18</sup> mentioned having seen a case of osteomalacia in the bones of an ancient Peruvian, and MacCuidy<sup>17</sup> contributed another case

*Osteoporosis of the Surface of the Cranium*—A symmetrical osteoporosis on the outer surface of the skull, chiefly of the parietal and frontal bones, giving a startling effect (fig 1), is often seen in the skulls of American Indians and to a smaller extent in those of other races. Though physical anthropologists are familiar with it, the condition seems to be little known to general pathologists.<sup>31</sup> If it is figured in any of the textbooks of pathology, I have overlooked this fact. The omission is no doubt due to its being extremely rare in the modern white race, if it occurs at all. For that reason, the subject will be considered in some detail.

All of the large collections of Indian bones that I have been able to examine have one or many examples. It seems to occur more abundantly in certain localities than in others not far removed. I have obtained the impression that it was more common in ancient Peru than in any other part of America. Hrdlička<sup>16</sup> found it occurring frequently in skulls from the coastal regions of Peru, but not in those from the mountains. In one lot of Peruvian remains, he encountered osteoporosis in eight of 262 skulls from adults, and in three of sixteen skulls from children. I had the opportunity to examine some 176 skulls from Peru at the Field Museum, Chicago, most of them from adults, and noted four with osteoporosis, counting only those in which the condition was marked. The most typical case occurred in the skull of a child. Another of the four cases (no 168716) was singular in that it involved most of the skull, including the face, except the parietals. Sylvanus G. Morley and G. D. Williams informed me, in personal communications, that it was exceedingly common among the Mayas of Yucatan, chiefly in young persons. It was also frequent in New Mexico and Arizona. Among fifty-four skulls at the American Museum of Natural History, New York, most of them from the southern part of the United States and from the West Indies, I found one skull showing osteoporosis. It was from Georgia. At the Field Museum, Chicago, I examined fifty-four skulls from Cahokia, Ill., and thirty-three from Cross County, Ark., and found one well marked case from the latter locality. At the Museum of the Buffalo Society of Natural Sciences I examined eighty skulls from

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31 I cannot find any reference to it in Pommer. *Origin and Diagnostic Significance of Osteoporosis*, *Arch f klin Chir* **136** 1, 1925, nor in the referat of the German Pathological Society on osteoporosis, *Centralbl f allg Path u path Anat* **35** 258, 1924-1925. Osteoporosis, in general, may, of course, result from many different causes. It is not surprising that metastatic tumors of the cranium occasionally produce appearances somewhat like the symmetrical osteoporosis under discussion. A case was reported by Roman. *Beitr z path Anat u z allg Path* **53** 69, 1912.



Fig 1—Symmetrical osteoporosis of the upper surface of the cranium. This seems to have been an active case. The sutures are involved to some extent, which is unusual. The skull is that of an adult or a young adult. The size is slightly reduced in the photograph. The resemblance of the surface to pumice stone may be noted. Figure 2 shows a roentgenogram of the same skull. The specimen is an old one, evidently long buried. It probably belonged to an Indian of the State of New York, but there is no definite record as to its source. It is now in the museum of the University of Buffalo (4367). The inner surface of this skull is nearly smooth and is normal. The skull shows a moderate degree of deformation, doubtless unintentional and common among many tribes of Indians.

western New York and the adjacent part of Ontario and found no case of symmetrical osteoporosis. Figure 1 shows a specimen of uncertain origin probably from a New York State Indian. It presents one of the most marked cases of osteoporosis that I have seen, and the amount of osteophytic growth is suggestive of tumor formation. Although it is from an adult or a young adult, I should call it an active case. Figure 2 is a roentgenogram of the same skull. (All the allusions that I have made or shall make in this section to skulls of American Indians refer to material that is ancient in the sense that it may be from 100 to 200 years old to 1,000 or 2,000 years old. It is frequently if not usually impossible to give an approximate date to such material.) Adachi<sup>32</sup> gave beautiful illustrations of symmetrical osteoporosis occurring in a Dyak and in an ancient Egyptian. Wood-Jones<sup>33</sup> described what may be the same thing from ancient Egypt, though his description and illustration leave one somewhat in doubt. The condition described by him, he thought, might have been caused by carrying water jars on the head. Another case in an Indonesian was reported on by Bickel,<sup>33</sup> who gave a survey of the literature. T. Wingate Todd, of Western Reserve University, Cleveland, informed me (in a personal communication) that he had seen the condition once (in the skull of a child, not rachitic) in about 600 modern negro skulls studied by him. The skull of a child 8 years old, found in France, apparently of the Gallo-Roman period, was described by Saint-Perier<sup>34</sup> as an example of congenital syphilis, from the description and the illustration, this seems to me to be a case of symmetrical osteoporosis. Parrot<sup>35</sup> long ago gave descriptions of what he called hereditary syphilis of the bones of the skull, which, in some respects, suggest symmetrical osteoporosis. Three specimens, probably presenting the latter condition and not syphilis, coming from Peru, were mentioned by Parrot as examples of syphilis of ancient American origin.

Though symmetrical osteoporosis is most frequent and most marked on the parietal and frontal bones, the occipital bone is often involved. The temporal bone and sphenoids are involved less frequently and the bones of the face very rarely. By the courtesy of A. Hrdlička, of the United States National Museum, Washington, I have been able to examine the bony remains of three young infants from New Mexico, showing marked osteoporosis of the cranium, in which a considerable part of the rest of the skeleton had been preserved. A similar osteoporosis was well marked on the surface of the bodies of

32 Adachi, B. *Die Porosität des Schädeldaches*, *Ztschr. f. Morph. u. Anthrop.* **7** 373, 1904.

33 Bickel, B. *Ztschr. f. Ethnol.* **49** 102, 1907.

34 Saint-Perier. *Bull. et mem. Soc. d'anthrop. de Paris* **5** 31, 1914.

35 Parrot, Jules. *Les lésions osseuses de la syphilis héréditaire*, *Tr. Path. Soc. London* **30** 339, 1879.

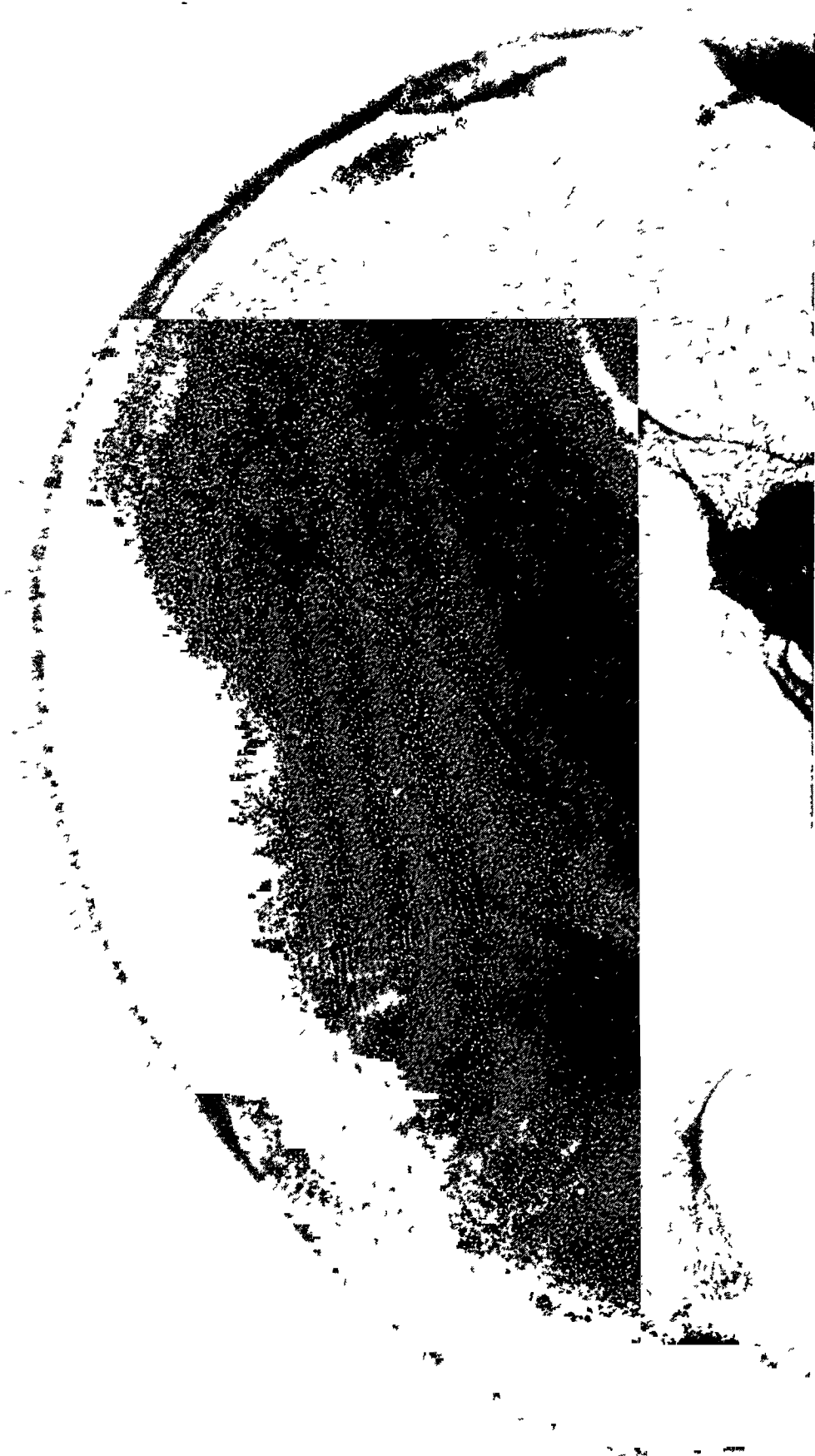


Fig 2—The skull with symmetrical osteoporosis shown in figure 1, natural size A roentgenogram of a skull in the Peabody Museum, Cambridge, Mass, gives practically an identical picture

the vertebrae, and it appeared also, in traces, externally on the long bones, there was no irregularity of the teeth. MacCuddy<sup>17</sup> told of a case in an ancient Peruvian who at death was probably 70 years old, who had been trephined through an area of osteoporosis of the skull, and who had osteoporosis of the long bones and showed evidences of fractures. The condition is evidently the same as that called *cribra parietalia* by Adachi.<sup>18</sup> A similar condition seen on the orbital plate (*cribra orbitalia*) and a somewhat similar condition of the inner surface of the skull (*cribra cranii*) will be mentioned in an ensuing paragraph. Symmetrical osteoporosis of the ancients was decidedly most common in childhood. The inner surface of the skull is almost never affected. The areas involved, in some cases, are of insignificant size and in others include the greater part of the upper surface of the cranium. Their symmetrical distribution is notable. The sutures are usually avoided. The appearance of the surface has been likened to pumice stone or to coral or to fine sponge or to moss. The outer table may be altogether wanting, while the cancellous bone of the diploe with enlarged spaces, up to 2 mm. or a little more in diameter, is level with or protrudes a little above the general surface. This lack of depression, or protrusion owing to new growth of bone, distinguishes osteoporosis from the appearance of a portion of skull from which the outer table has been accidentally removed or eroded, there is a slight superficial resemblance between them. In cases like this, the condition is regarded by Hrdlička<sup>16</sup> as active, in other cases, in which the condition may have been arrested or healed, a relatively smooth thickening over the region involved is seen, while the outer table remains perforated with holes from the size of pinpoints up to a diameter of 2 mm. or more. Such an appearance suggested the name of *cribrum* (sieve). Hrdlička believed that symmetrical osteoporosis began to show itself in infancy, that the underlying condition, whatever it may have been, was frequently fatal, that the process began in the roof of the orbit or on the frontal bone, and extended to other parts of the upper surface of the cranium, and that, in some cases, there was a recovery, but with the relics of the condition often remaining throughout life (fig. 3).

In general, the distribution of the lesions reminds one strongly of that described by some German authors for the lesions of rickets of the skull—symmetrical and avoiding the sutures. These lesions do not, however, occur along the margins of the bones as the lesions in rickets are stated to do. But if I understand correctly, Kaufmann's<sup>36</sup> sketch

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<sup>36</sup> Kaufmann. *Lehrbuch der speziellen pathologischen Anatomie*, Berlin and Leipzig, Vereinigung wissenschaftlicher Verleger, 1922, vol. 1, p. 902, fig. 515. Wakeley and Bunton. *Surgical Pathology*, New York, William Wood & Company, 1929, p. 269.

showing the regions affected by rickets on a child's skull, the areas of involvement are the same as those that one most often sees affected in symmetrical osteoporosis

The condition that Wood-Jones<sup>37</sup> discussed under the title of "Cranial Ulceration," which was frequent in ancient Nubia, and which he attributed to the carrying of water jars on the head, corresponds, in some respects, to symmetrical osteoporosis, in others, it does not. Apparently, in some of his cases, the soft parts over the skull were preserved, permitting the observation that ulceration had occurred. If symmetrical osteoporosis of the upper surface of Egyptian skulls was mentioned by Smith, Derby, Ruffer or Oettinger, I overlooked the references. Adachi's case has been referred to. Possibly, Wood-Jones worked in a locality where it was unusually frequent, as it was in certain parts of America.

**Roentgenologic Observations** The radiating lines, like coarse bristles, replacing the outer table of the skull (fig 2) are evidently produced by the new bony growths, seen in profile. Two roentgenograms of skulls from Yucatan were sent me by Dr. E. A. Hooton, of Harvard University, one, of a case of acute symmetrical osteo-

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<sup>37</sup> Wood-Jones, F. Archeological Survey of Nubia, Report for 1907-1908, vol. 2, Human Remains, p. 203.

"On carefully examining a skull, it is by no means infrequent to see, either on the vertex or around and above the parietal eminences, some evidences of a more than usually abundant blood-supply to the outer table of the bone. Minute points stand out upon the surface of the parietal bone, and the mouths of small vascular canals are dotted about upon the parietal eminences, and upon the surface of the skull above them. Such a condition is very common among skulls of all periods, and it may be strictly limited to this area of the parietal bones, or it may be much more diffuse. It may be easily overlooked in its earlier stages, and so in some measure its probable, and simple, etiology may be lost sight of. The condition, however, may not be limited to this stage of hyper-vascularity of the surface of the bone. In some cases minute ulcerations of the outer table are seen at the point of maximum intensity of the process, and in other cases this ulceration has spread until it is the dominant feature in the picture.

"At times the process becomes so acute that necrosis of the outer table of the skull has taken place, and portions of the scalp and cranial wall have sloughed away. When this condition is seen only in its advanced stages it is one that naturally suggests some severe disease, and it is not surprising that the syphilitic virus has been invoked as the causative factor yet it is accompanied by none of the other signs of the disease, and a careful study of its etiology shows it to be a process quite distinct from any specific infection. The evidences of cranial periostitis in these cases are usually bilateral, and approximately symmetrical, and the ulceration—when the process is advanced—is at times symmetrical, too. It was noticed from the outset of this investigation that the condition was more common among females than among males, and in Cemetery 23 (for instance) the condition occurred as often as five times in the twelve females bodies."

The author goes on to discuss the possible relation of this condition to the carrying of water jars on the head. The drawing that he gives (his fig. 66), as has been stated, is suggestive of the osteoporosis that is the subject of this section.

porosis gives a picture nearly identical with that seen in figure 2, the other, of a case of healed symmetrical osteoporosis, gives a picture similar but less distinct (Roentgenograms of the bones shown in figures 3 and 4 give no more than suggestions of these lines) Cooley, Witwer and Lee<sup>37a</sup> described similar changes in the skull in certain anemias of childhood Di M C Sosman, of the Peter Bent Brigham Hospital, Boston, found a picture like this in the skulls of negroes with



Fig 3—Symmetrical osteoporosis of the upper surface of the skull a healed case, from the Chicama Valley, Peru (after Hrdlicka Smithsonian Collections **61** 57, 1914)

sickle-cell anemia and of white men, usually Greeks or Italians, with von Jaksch anemia (personal communication) I have seen roentgenograms of two cases of metastatic tumor of the cranium that gave radiating lines somewhat like those described

<sup>37a</sup> Cooley, Witwer and Lee Anemia in Children with Splenomegaly and Peculiar Changes in Bones Report of Cases, *Am J Dis Child* **34** 347 (Sept) 1927



**Histologic Changes in Symmetrical Osteoporosis** Through the courtesy of A. Hrdlička, I have been enabled to make sections from two moderately well marked cases of osteoporosis in a parietal and a frontal bone of young children, Indians of Arizona and Utah (figs 4 and 5). The marrow being gone, one could study only the framework of the decalcified bone. The spaces of the cancellous bone of the diploe were large. They opened widely on the surface, and gave the impression that the marrow protruded under the periosteum. These openings were evidently the equivalent of those present on the normal skull for the passage of vessels, well developed on the parietal bones of normal infants.



Fig 4—*A* represents symmetrical osteoporosis of the frontal bone of a child, an active case, from Utah, *B*, a very low power magnification of a section from the bone shown in *A*. The osteophytic growth on the outer table may be noted

but of exaggerated size in symmetrical osteoporosis. In one of the skulls, in which the disease was shown still acute and progressive (fig 4 *A*), the outer table could barely be traced through the area involved, and new cancellous bone projected above the general surface. The impression obtained from these sections was that they had much similarity to the periosteal formation of osteoid tissue and bone seen in rickets<sup>38</sup>. Sec-

38 One of the illustrations of sections of the skull from cases of rickets in Shattock's article on "Morbid Thickening of the Calvaria," etc (Tr XVIIth Internat Cong Med London, 1913 sec 3, Pathology, p 3) is strikingly like the picture from one of my sections (fig 4 *B*).

tions were made from the ribs of two other ancient Indians of New Mexico, both having marked osteoporosis of the parietal bones. The large size of the spaces of the cancellous bone of these ribs was striking (fig 6). There were points where the rib was little more than a shell that once contained marrow. The junction of the rib with the cartilage was not like that seen in rickets. These changes were suggestive of some systemic disorder affecting the bone marrow in general. I do not know of any studies on the histologic changes in which the

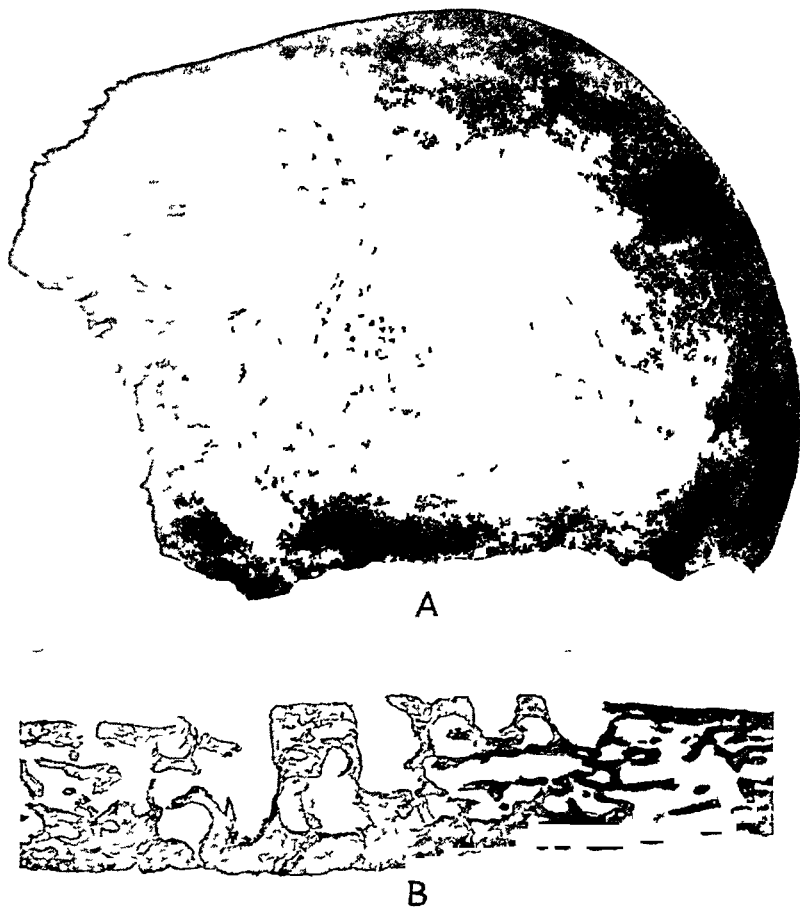


Fig 5—*A* represents symmetrical osteoporosis of the parietal bone of a child from Arizona, a practically healed case, *B*, a low power magnification of a section from the bone shown in *A*. The openings are in the outer table.

marrow and the periosteum were found preserved. It is possible that such material could be obtained from autopsies on modern Indians.

Von Hansemann,<sup>39</sup> in his monograph on rachitis of the skull, considering chiefly conditions found in apes kept in captivity, described and

<sup>39</sup> Von Hansemann, David. *Die Rachitis des Schädels*, Berlin, A. Hirschwald, 1901.

illustrated some conditions that are like the symmetrical osteoporosis of human skulls, while other conditions that he described, I should think, were more like osteitis deformans (Paget's disease) or leontiasis ossea. The tendency of the condition shown in his apes to spread to the bones of the face is not exhibited in the symmetrical osteoporosis under discussion, which, as Hrdlička<sup>16</sup> pointed out, rarely appears on the face. T. Wingate Todd informed me (personal communication) that he found symmetrical osteoporosis in the skull of a monkey, *Lagothrix lagotica*, that had calcium deficiency but not rickets.

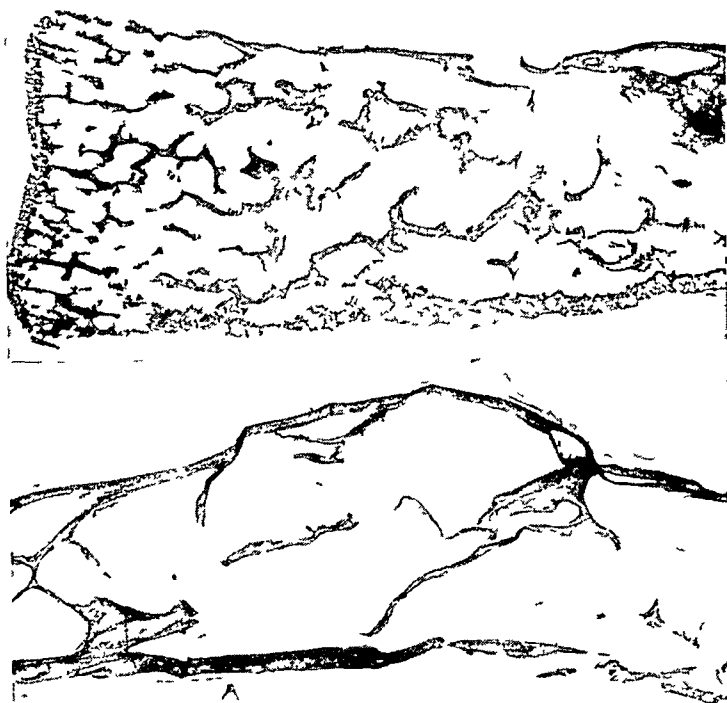


Fig 6—Very low power magnification of sections near the ends of the ribs of two skeletons that showed marked symmetrical osteoporosis of the skull. It may be noted that the costochondral junction, shown in the upper section, is not like that of rickets. The skeletons were those of Pueblo Indian children of New Mexico.

Practically no information exists as to the causation of symmetrical osteoporosis. Irritation and pressure have been mentioned as possible causes. The influence of toxic disorders (Hrdlička), endocrine disorders, disturbances of calcium metabolism, lack of some vitamin and other dietary deficiencies suggest themselves as possibilities. The food of the Indians and of the poor people among ancient Egyptians viewed from the modern standpoint was miserable and the supply precarious. As for the sedentary Indians, both of North and of South America, maize or Indian corn was the most important item in their food and it

may be worthy of note that maize is said to be deficient in the anti-scorbutic vitamin C and probably in the antirachitic vitamin D. On looking at Wissler's<sup>40</sup> map of the food areas of the New World, it is seen that his "area of intensive agriculture" corresponds closely with the regions from which most of the cases of symmetrical osteoporosis have been reported. However, rickets, as one now sees it, seems to have been infrequent among the Indians. There was certainly an abundance of sunlight available in most of this area. The infant's body, however, would be little exposed if it was constantly wrapped up. The examinations which I have given are the only ones that I know of for the eastern half of the United States, they indicate that symmetrical osteoporosis occurred there but was not common. In this area, agriculture was practiced perhaps less intensively, and here, again, maize was the staple product, for the most part.

The results of roentgen examinations of the skull in anemias of children are most suggestive. It is to be hoped that the relation of the condition described in these anemias with symmetrical osteoporosis may be determined by further study. Tello<sup>41</sup> discovered a Peruvian skull, now in the Warren Museum, Harvard Medical School, Boston, in which trephining had been performed through an area of osteoporosis, which, of course suggests that the operation had been done to relieve pain. As mentioned later, MacCurdy and Muniz and McGee reported similar cases, and there is another in the United States National Museum, Washington, D C (266064 Peru). It has occurred to me that the pressure produced on the occiput of the Indian baby resting on a head board would tend to create a venous hyperemia in the parietal and frontal regions, the venous outlets for the posterior region being impeded. Such hyperemia might cause a localization of osteoporosis over the parietal and frontal bones, not operating as a cause by itself but in combination with some of the causes enumerated. In cases of intentional deformation, pressure was made also on the frontal region, and sometimes about the sides of the head, so that one would expect venous hyperemia of the vertex to have been even more marked. The use by many Indians of a "tump-line" passing over the forehead to carry heavy loads must have exerted strong pressure on the frontal region, and might be considered as a factor in young persons, but I should not lay much stress on the tump-line.

Cribra orbitalia is the name given by Welcker<sup>42</sup> to a condition much like cribra parietalia (symmetrical osteoporosis) but located on the

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40 Wissler Clark. *The American Indian*, ed 2. New York, Oxford University Press, 1922. p 2.

41 Tello, J C. Prehistoric Trephining Among the Yauvos of Peru, *Proc Internat Cong Americanists* London 1913, pt 1, p 75.

42 Welcker. Cribra orbitalia. *Arch f Anthropol* 17 1, 1888.

upper wall of the orbit and usually covering a much smaller area. It is found often in children and has been described as occurring in Egyptians, ancient and modern, in Japanese, in Europeans and in Negroes and is seen in the skulls of American Indians. According to Toldt, quoted by Oetteking,<sup>43</sup> there is an increased formation of spongy bone, the outer table is but slightly developed, there is a change in the circulation so that blood flows through the periosteal veins rather than through those of the diploe, and a spongy new growth of bone of the nature of osteophytes is formed, otherwise the orbital plate is thin and without diploe.

*Cribra crani* (Waldeyer) is a condition affecting the inner surface of the skull, described at length by Koganei,<sup>44</sup> who regarded it as related to *cribra orbitalia*, but was uncertain as to *cribra parietalia*. His *cribra crani* is frequent in children, and it occurs in modern Germans and Japanese, as well as in ancient peoples. It is commonest on the inner surface of the frontal bone, and seems related to the impressions made by the blood vessels. There is an abundance of marrow in the spongy bone, and in recent cases the formation of new layers of bone can be recognized. He regarded it as similar to the osteophytes of the puerperium.

The descriptions and illustrations of the histologic changes in *cribra orbitalia* and *cribra crani* are like the pictures that I obtained in symmetrical osteoporosis.

*Fractures and Injuries*—Whether or not the conditions under which men lived in earlier times were more conducive to bodily injuries than those of modern civilization might be an interesting if not a profitable subject for speculation. It is certain that every large collection of ancient or prehistoric bones has numerous examples of fractures, healed or otherwise.

Perhaps as celebrated as any fossils that have ever been found are the bones of *Pithecanthropus* from Java, usually ascribed to the late tertiary period, therefore antedating the glacial period. If not the bones of a man or of a direct ancestor of man, they are at least those of a cousin of the ancestor of man. The left femur presents an enormous, irregular exostosis on the inner side of the upper third, evidence of fracture is not present. I have seen only casts and photographs of this femur, but the abnormal and redundant new growth of bone is so like that occurring about many healed fractures that I should suppose it had been caused by injury. Dubois,<sup>45</sup> the discoverer of the specimen,

<sup>43</sup> Oetteking. *Kraniologische Studien in Aegypten*, Arch f Anthrop **36** 49, 1909.

<sup>44</sup> Koganei, Y. *Cribra crani und Cribra orbitalia*, Mitt a d med Fak d k Univ zu Tokio **10** 113, 1913.

<sup>45</sup> Dubois, E. *Ueber die Hauptmerkmale der Femur von Pithecanthropus erectus*, Anthrop Anz **4** 131, 1927.

described marks at various points about the upper end of the femur that he ascribed to the teeth of a crocodile, which I interpret as giving support to the supposition that the exostosis was caused by injury

The Neandertal race belonged to the latter part of the glacial period, and the famous but incomplete skeleton from which this race was named is now in the Provincial Museum, Bonn. The left humerus and ulna also show deformity probably caused by injury.<sup>46</sup> Among the bones of an early type of Neandertal man found at Krapina, Croatia, there is a clavicle with a well united fracture.<sup>47</sup> The Rhodesian skull from South Africa, of undetermined but ancient age and of extraordinarily brutal type, resembles the Neandertal skulls in many respects. It shows evidence of a severe injury above one ear, which was probably followed by suppuration.<sup>48</sup>

One of the two skeletons found at Obercassel in Germany, referred to the late paleolithic (Magdalenian) period, bears the marks of an old injury on the left parietal bone and of an old united fracture of the right ulna.<sup>49</sup> One of the group of skeletons discovered at Cro-Magnon (Aurignacian) bears the plain marks of a blow on the forehead. These bones belong to the early part of the period of the cave artists, which is roughly around from 20,000 to 30,000 years ago.

There is nothing surprising in these facts unless it is that the evidence of injury should have been preserved from such remote times.

Wood-Jones<sup>13</sup> described a great number and variety of fractures found in the bones of the ancient Nubians. He made interesting comparisons between the incidence of these fractures in the various parts of the body and the incidence of fractures in the corresponding parts of the body in the great cities of the present day. He found the results of whatever treatment was used good, and was especially amazed at the evidences of recovery from extensive fractures of the skull. He remarked that sepsis rarely followed even severe fractures that must have been compound. He gave sketches that adequately illustrate the distribution and the types of the fractures.

MacCurdy<sup>50</sup> called attention to the large number of fractures of the skull among the ancient Peruvians, which he attributed to the impacts of the war clubs used in their hand-to-hand combats.

46 Hrdlička, A. The Most Ancient Skeletal Remains of Man, Rep. Smithsonian Inst. for 1913, Washington, 1914, p. 520.

47 Gorjanovic-Kramberger, Karl. Der Diluviale Mensch von Krapina in Kroatien, Wiesbaden, Kreidel, 1906.

48 Keith, Arthur. The Antiquity of Man, ed. 2, London, Williams & Norgate, 1925, p. 417.

49 Verworn, Bonnet, and Steinmann. Der diluviale Menschenbefund von Obercassel bei Bonn, Wiesbaden, 1919.

50 MacCurdy, G. G. (footnote 17, p. 236).

Many museums have bones of the neolithic and later periods with flint or bronze arrow or spear points still embedded where they lodged. I have seen numerous specimens of this kind among bones of American Indians. Such relics have a certain dramatic quality, but they do not give any new information as to the pathologic changes in bone. The results of injuries of bone in ancient times do not seem in any way different from those that are observed today. Cases of ankylosis and of dislocation have been found many times among prehistoric bones, differing in no respect from those that one sees at the present time.

Elliott Smith<sup>51</sup> described and illustrated with excellent plates a fracture of the femur and one of the forearm that were enclosed in splints in a skeleton from tombs of the fifth dynasty in Egypt, that is, from 4,000 to 5,000 years ago. Another and later example was recorded by Wood-Jones<sup>52</sup>.

Moodie<sup>52</sup> described and gave good illustrations of a well preserved bandage remaining on an ancient head from Peru, consisting of cotton cloth placed over the occiput and held in position by woolen cord.

Wood-Jones<sup>53</sup> reported on an examination of the bodies of 100 men executed in Nubia in Roman times, which exhibited unusual results, apparently from hanging, which are of interest to students of medicolegal problems, and in his works on the Archeological Survey of Nubia, he cited many other examples of injuries.

*Primitive and Prehistoric Trephining*<sup>54</sup>—Trephined skulls from neolithic graves in France were found some time before their nature was understood. The story of the manner in which they came to be correctly interpreted is of some interest, I have condensed it from MacCurdy<sup>55</sup>.

The pioneer archeologist of America, E. G. Squier, while in Peru, obtained an ancient Inca skull that had been trephined by making two pairs of parallel incisions in the skull at right angles to each other. Squier submitted this skull<sup>56</sup> to Broca, who recognized it as an example of trephining, later, Broca realized from this specimen the true nature of the European specimens. Prunieres about the same time (1870-

51 Smith, G. E. The Most Ancient Splints, *Brit. M. J.* **1** 732, 1908.

52 Moodie. *Ann. M. History* **8** 69, 1926.

53 Wood-Jones. *Brit. M. J.* **1** 736, 1908.

54 This subject has been discussed in many articles, only a few of which can be mentioned here. The citations that I am making give many references to the literature.

55 MacCurdy (footnote 8, first reference, vol 2, p 165, footnote 17, p 236). These contributions include good plates.

56 According to MacCurdy, this skull is now in the American Museum of Natural History, New York. A good photograph of it appeared in Muniz and McGee. *Primitive Trephining in Peru*, *Rep. Bur. Am. Ethnol.*, Washington **16** 11, 1894-1895.

1880) described trephining in neolithic skulls Broca used a paleolithic chipped flint to trephine the skull of a 2 months old dog, it was done by the scraping process and required eight minutes, the wound healed promptly The two methods just mentioned appear to have been those most commonly used, rarely cauterization may have been employed, or possibly, as suggested by Lucas-Championniere, a series of perforations close together and in the form of a circle, to permit the removal of a round plate of bone <sup>57</sup>

MacCurdy gave a photograph of a Peruvian skull (fig 7) which he thought held the record, and probably with justice, for it had been successfully trephined five times Many cases of trephining are found in which healing had not taken place, the patient succumbing to the operation or to the condition for which the operation was performed The openings that do not show signs of healing may have been made post mortem as part of some ritual or to secure bone amulets

Muniz and McGee <sup>56</sup> thought that the surgery in Peru "was crude in plan and bungling in procedure" They admired the vitality of the patient, rather than the technic of the operator They believed that the mortality must have been high (Their monograph includes good plates, some of them showing the removal of a rectangular plate of bone by two pairs of parallel grooves at right angles to each other) MacCurdy, on the other hand, was impressed with the skill of the Peruvian surgeons, and Moodie said that healing often seemed to have been rapid

Evidence of prolonged suppuration following the operation is not common Proof of the method by which the operation was performed is not usually preserved in the old bones In the skulls that have healed, the edges of the openings are usually round or beveled

The frontal and parietal bones were the parts usually operated on The forehead low down, and the occipital and the temporal bones were only rarely attacked A healed injury or a large persistent parietal foramen may look somewhat like an example of trephining

Several different purposes have been supposed to have animated the operators, who were doubtless the medicine men of the tribe or their equivalent First, the object may have been to permit the escape of evil spirits from the skull in cases of epilepsy or insanity Second, the operation may have been done to cure local disease or in the treatment of fractures, or third for the relief of headaches A few skulls with symmetrical osteoporosis that had been trephined have been found in Peru Tello,<sup>41</sup> MacCurdy <sup>17</sup> and Muniz and McGee <sup>56</sup> gave illustrations of this, and there is a skull showing it in the United States National

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<sup>57</sup> A good photograph of a skull from Peru in which this method had been tried is given in Moodie R L Ann M History 9 277 (his fig 19 B), 1927





Fig 7—A skull that has been successfully trephined five times. It is that of an adult male of Patallacta, Peru (after MacCurdy, G G. *Am J Phys Anthropol* 6: 265, 1923)

Museum, Washington (266064) MacCurdy<sup>17</sup> believed that he had seen clear evidence that in Peru trephining was frequently done for the relief of fractures probably the result of combats, and perhaps in the treatment for disease Tello<sup>41</sup> offered substantially the same opinion Moodie<sup>57</sup> stressed the use of the sling by the old Peruvians, as frequently causing fractures of the skull, and the attempts to relieve depressed fractures by trephining Moodie<sup>58</sup> quoted Hrdlička to the effect that trephining was done for surgical reasons, also to the effect that the opening was sometimes covered with a plate made of gourd or of shell or of silver At the meeting of the International Congress of Americanists in New York, September, 1928, Julio C Tello, curator of the Peruvian Archeological Museum, Lima, exhibited two remarkable skulls, in one of these, a thin polygonal plate of beaten gold had been laid over the circular hole in the skull, apparently healing had taken place with this plate in position, although it was not possible to be certain as to this point, for the specimen was shown as it came from the ground, without cleaning The other skull was that of a subject who must have died shortly after the operation, a suture of cotton string was still present in the scalp over the opening in the skull Posansky,<sup>59</sup> from his observations in the highlands of South America, stated that the present-day Indians perform severe operations after having stupefied the subject with a native brew of alcohol and by the local application of coca leaves He thought that trephining was performed under similar conditions The use of coca leaves has been suggested by others, but, as strong solutions of cocaine are said not to have any anesthetic influence on the unbroken skin, the advantages obtainable from coca leaves used locally must have been limited When the scalp was lacerated, as in compound fractures, the patient must often have been rendered comatose by the injury

Prehistoric trephining was probably carried out more frequently in Peru than in any other part of the world Muniz and McGee<sup>56</sup> found nineteen cases of it in about 1,000 skulls, while MacCurdy<sup>17</sup> reported that in a series of 250 craniums, 18 per cent had been trephined Bandelier<sup>60</sup> found sixty-five skulls trephined (by scraping) in about 1,200 from Bolivia According to Bandelier, trephining was still practiced in Bolivia in 1904, though rarely and secretly Among 176 skulls from Peru at the Field Museum, Chicago, I found two examples of trephining, one fresh and one healed

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58 Moodie (footnote 52, p 397)

59 Posansky, A Ueber Trepanieren und kunstliche Verunstaltungen an Amara Schadeln, *Arch f Anthrop* **56** 158, 1924

60 Bandelier, A Aboriginal Trephining in Bolivia, *Am Anthrop N S* **6** 440, 1904

Trephined skulls from the Tarahumara Indians of northern Mexico have been reported<sup>61</sup> Two trephined skulls found in New Mexico were described by Shapiro<sup>62</sup> The United States National Museum, Washington, has one from Michigan (147272) Greenman<sup>63</sup> mentioned examples from Michigan Smith<sup>64</sup> reported on such skulls from Canada Others may have been described, but these are sufficient to show that while examples are found in North America, they are rare

Numerous trephined skulls have been found in France, Switzerland, Bohemia, Moravia and other parts of Europe chiefly western Europe, including Denmark and Sweden (Fuist<sup>5</sup>) and the Canary Islands Parry<sup>65</sup> was able to learn only of three found in England, and one of these was doubtful Most of the European specimens belong to the neolithic period, a few are said to be of the bronze age and even of the iron age<sup>66</sup> The practice may have continued down to historic times

A somewhat doubtful specimen from Egypt, 200 A D, was reported by Ruffer,<sup>67</sup> and another was reported by Derry,<sup>68</sup> who, however, was of the opinion that the opening was either congenital or, more probably, due to a dermoid cyst The absence of trephined skulls from Egypt is noteworthy when one realizes that many thousand Egyptian skulls have been studied by competent observers

Ruffer gave a valuable review of the knowledge on this subject, including trephining as now practiced by the Kabyles of North Africa and other modern tribes<sup>69</sup>

*Cranial Scars*—A rare lesion of neolithic skulls from dolmens in France was described by Manouvrier<sup>70</sup> It consists of some erosion and

61 Lumholtz and Hrdlička, A. *Am Anthropol* **10** 389, 1897

62 Shapiro *J Am Mus Nat Hist* **27** 266, 1927

63 Greenman *Am Anthropol N S* **28** 312, 1926

64 Smith, H J *Am J Phys Anthropol* **7** 447, 1924

65 Parry *Lancet* **1** 1699, 1914

66 MacCurdy (footnote 8, vol 2, p 405) Matiegka, J *La trepanation et autres operations sur la tete a l'epoque prehistorique sur la territoire de la Tchecoslavique, Anthropologie, Prague* **6** 41, 1928 Sudhoff, Karl *Medizin in der Steinzeit, Ztschr f arztl Fortbild* **6** 196, 1909

67 Ruffer (footnote 1, second reference, p 196), *Some Recent Researches on Prehistoric Trephining, J Path & Bact* **22** 90, 1918

68 Derry, D E *J Anat & Physiol* **48** 417, 1914

69 Recent studies giving methods of trephining now used by savage tribes are Sarasin, F *Abstr, Anthropologie* **29** 151, 1918-1919 Wolfel, D J *Die Trepanation Studien uber Ursprung, Zusammenhange und Kulturelle Zugehorigkeit d Trepanation, Anthropos*, 1925, vol 20, brief review by MacCurdy *Am Anthropol* **29** 118 1927

70 Manouvrier quoted by MacCurdy, G G *Prehistory Surgery, A Neolithic Survival, Am Anthropol N S* **7** 17, 1905 also mentioned in MacCurdy (footnote 8, vol 2, p 166) A good photograph of the lesion is shown in the article on prehistoric surgery

some new formation of bone on the upper surface of the skull in the form of a line beginning just above the anterior curve of the frontal bone extending to the posterior part of the parietal bones, where it runs into a lateral branch making a kind of T (sincipital T). The scars may be deep enough to produce a form of trephining. The scars are believed to have been made by lesions of the scalp, probably cauterization, deep enough to have affected the periosteum. Quotations that are given from Avicenna and Albucaasis indicate that such cauterization was employed in their day in the treatment for epilepsy and melancholia. It is suggested that a form of treatment used in neolithic times survived and was still practiced in the middle ages.

Somewhat similar oval scars in the region of the anterior fontanel have been described as occurring on the crania of the Guanches, ancient inhabitants of the Canary Islands, rarely these give evidence of grave suppuration, obviously, they were produced by some form of injury. Historical accounts indicate that scarification for the relief of pain was used by the Guanches.<sup>71</sup>

A skull from Peru that may be an example of some kind of scarification was described by Moodie.<sup>72</sup> MacCurdy<sup>17</sup> saw what he considered a somewhat doubtful case of cauterization in a skull from Peru.

*Osteomyelitis, Osteitis and Periostitis*.—Practically all reports on the diseases shown in ancient bones refer to the bone changes known under one or all three of these names. This statement applies to neolithic Europe, to Egypt and to North and South America. It is not always easy to distinguish between postmortem erosion of old bones by natural causes and destruction produced by inflammation of bone. The difficulty of determining, without clinical history or other aids, whether the changes in an isolated dried bone were produced by suppurative osteomyelitis or by tuberculosis is evident to any pathologist. Wood-Jones<sup>13</sup> remarked on the rarity of evidence of infection following even severe fractures. Remembering the numerous specimens showing destructive inflammation of bone in museums of modern pathology, I have, on the whole, been impressed with the rather small amount of material of the same kind that has come down from ancient times. An exception, however, may be made of the alveolar processes of the jaws, which will be considered in connection with the subject of ancient teeth. Wood-Jones reported a few cases of destructive disease of bone, among

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71 Lehmann-Nitsche, Robert. *Lesions de crânes des Iles Canaries*, *Rev del Museo de la Plata* **11** 211, 1903. This article gives references to the literature, and discusses the lesions on the skulls of the Guanches, and describes the method of scarification in detail. Bockheimer, Bregmanarben und ihre mutmassliche Entstehung nach Untersuchungen an Guancheschadeln, *Arch f Anthrop* **54** 131, 1922. Bockheimer's references constitute a review of the literature.

72 Moodie, R. L. *Am J Phys Anthrop* **4** 219, 1921.

them one of perforation of the hard palate due to chronic rhinitis. His remarks on osteitis of the upper surface of the cranium are referred to in the section on symmetrical osteoporosis. Smith and Dawson<sup>6</sup> remarked that mastoid disease was frequent in ancient Egypt and Nubia, it is occasionally seen in Indian bones from North and South America. Irregular thickening of the long bones, especially the tibia, has been found common in ancient Indian remains both from North and South America, and has been described by many investigators. The possibility that the condition may have been caused by syphilis was brought forward long ago and has occasioned much controversy, with indecisive results.

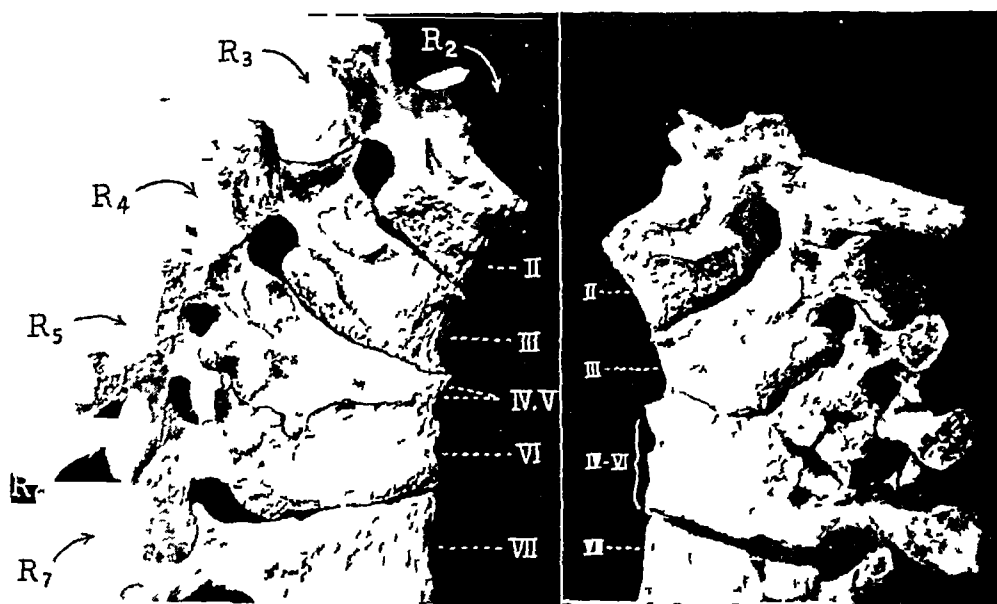


Fig 8—Dorsal vertebrae of a neolithic skeleton found near Heidelberg, Germany, described by Bartels (*Arch f Anthrop* 6 243, 1907) as an example of Pott's disease. Reproduced by permission of the editor of the *Archiv für Anthropologie*.

*Syphilis*—It is my intention to consider the subject of prehistoric syphilitic bone disease in a separate paper, which is now in preparation. It will be sufficient to say that at the present moment I cannot learn of any published case that is known to antedate the year 1500 A.D. and that can confidently be pronounced syphilis of bone.

*Tuberculosis*—The evidence for the existence of tuberculosis in ancient times is derived from a small number of cases, and much of this evidence is not convincing. A neolithic skeleton (fig 8) found near Heidelberg has been thoroughly described by Bartels,<sup>73</sup> and has been

<sup>73</sup> Bartels, Paul. Tuberkulose (Wirbelkaries) in der jüngeren Steinzeit, *Arch f Anthrop NF* 6 243, 1907.

referred to by several writers. The specimens came from a young adult. The bodies of the fourth and fifth dorsal vertebrae were almost entirely missing, the remnants of them were fused with the body of the sixth. As a result, there was kyphosis and some scoliosis to the right, narrowing of the spinal canal was not observed. Bartels believed that arthritis deformans might be excluded as an element in the case, and also fracture. The illustrations seemed to me not entirely convincing in excluding impacted fracture. Raymond<sup>72</sup> alluded to the frequency of tuberculosis in bones of the stone age, but did not tell of any new material, except a specimen showing what probably is spinal disease of the bronze age, from Nîmes, said to have been described by Poncet and Leiche. Fuist<sup>5</sup> stated that the earliest known example of tuberculosis in Denmark is one of spondylitis in a child of the twelfth century. In Egyptian remains, there is considerable evidence for tuberculosis, which was set forth by Smith and Dawson,<sup>74</sup> Derry and Smith<sup>75</sup> and Smith and Ruffer<sup>76</sup>. The material consists of a case of disease of the hip joint in a child from the fifth dynasty, about 2700 B C, and eight cases considered to be tuberculosis of the spine from ancient Nubia. One of these from the middle Nubian period, which I should judge to be around 2000 B C, was described by Derry<sup>77</sup> as follows:

A young woman about 21 years of age, whose lumbar vertebrae showed the following pathologic conditions. The first three vertebrae of the series were involved in the disease, which consisted in an ulceration of the centra of the vertebrae. The inflammatory process had completely destroyed the body of the second lumbar vertebra, which was firmly ankylosed to the first vertebra. The latter, owing to the loss of support from below, had fallen forward, so that its upper surface faced anteriorly, and it rested upon the surface of the third. The centrum of the latter was much eaten away by the disease, and formed, with the superimposed centrum of the first lumbar and the pedicles and laminae of the second, a large abscess cavity. When these three diseased vertebrae were placed in position with the other lumbar and lower dorsal vertebrae, a most striking picture of acute curvature incident to Pott's disease was revealed. No other signs of tubercular disease were met with in the rest of the skeleton.

Four other convincing cases of the Nubian archaic period are described by Derry<sup>78</sup>. Finally, there is the mummy (figs 9 and 10) described in detail by Smith and Ruffer,<sup>76</sup> that of a priest of Amen of

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74 Smith and Dawson (footnote 6, second reference)

75 Derry, D E, and Smith, G E. Bull Archeol Survey of Nubia, 1909, no 6, p 29

76 Smith, G E, and Ruffer, M A. Pottsche Krankheit an einer aegyptischen Mumie aus der Zeit der 21. Dynastie (um 1,000 V Chr.), in Sudhoff and Sticker. Zur historischen Biologie der Krankheitserreger, Giessen, 1910, no 3, reprinted in Ruffer (footnote 1, second reference)

77 Derry, D E. Bull Archeol Survey of Nubia, 1908, no 3, p 31

78 Derry, D E. Bull Archeol Survey of Nubia, 1910, no 5, p 21

the twenty-first dynasty, about 1000 B C. The specimen presented a marked angular curvature, projecting posteriorly, in the region of the eighth and ninth dorsal vertebrae. Extensive destruction of the last three or four dorsal vertebrae and of the first lumbar vertebra was evident. There had been some new formation of bone at the first lumbar vertebra. A swelling on the right, beginning at the last lumbar vertebra.



Fig. 9—A probable case of Pott's disease of the spine in the mummy of a priest of Amen, dating from the twenty-first dynasty in Egypt (from 1090 to 945 B C., according to Breasted). Figures 9 and 10 are reproduced by permission of G. Elliot Smith, who took the photograph, and for whom the drawing, figure 10, was made by Mrs. Cecil Firth.

vertebra, was traced down into the iliac fossa, without disclosure of any opening through the skin, it was regarded as a psoas abscess. This view seemed justified on account of the destruction in the region of the

right psoas muscle as compared with the left, although pus and cocci or bacilli could not be demonstrated (only molds). Trachea, larynx and bronchial lymph nodes were examined in sections for tubercle bacilli, and none were found. Although it is not stated that a search was made for tubercle bacilli in tissue from the psoas abscess, presumably such a search was made. This specimen seems as convincing as any ancient material could be expected to be, unless tubercle bacilli could be shown



Fig 10—Drawing of the priest of Amen whose mummy, showing what is probably Pott's disease, is seen in figure 9

to be present and this is not always easy to do in fresh cases of Pott's disease. Wood-Jones mentioned a lung of the Byzantine period thought to be tuberculous, though tubercle bacilli could not be found. Ruffer<sup>79</sup> reproduced figures from ancient Egypt that he believed were intended to represent the humpback of Pott's disease.

<sup>79</sup> Ruffer (footnote 28, first reference)



Although a number of reports on diseases of ancient bones of various parts of North and South America have been contributed, not many allusions have been made to anything that might be tuberculosis. Whitney,<sup>14</sup> who was a competent pathologist, described, without making a diagnosis, a case of destruction and ankylosis of the lower cervical and upper dorsal vertebrae from stone graves of Tennessee, and clay images representing hunchbacks. Means<sup>80</sup> mentioned what may have been a case of Pott's disease in mound builder remains from Ohio. Hrdlička<sup>81</sup> stated that "as yet no bones of undoubted pre-Columbian origin have been found that show tuberculous lesions, and such lesions are very rare in Indian bones dating from the period of the earliest contact with the whites."<sup>82</sup>

The excavations conducted by Kidder, of Andover, Mass., at Pecos, N M., have yielded a large amount of ancient osseous remains of the Pueblo Indians. Several specimens exhibiting what is thought to be tuberculosis of the vertebrae were found. Through the kindness of Hooton of the Peabody Museum, Cambridge, Mass., I have been able to give some of these specimens a brief examination, and they seemed to me to be promising. As has been stated, a report on the osseous material by Hooton,<sup>19</sup> to be issued by Phillips Academy, Andover, Mass., is in preparation.

*Arthritis Deformans*—New formation of bone about the joints and the accompanying deformities and ankyloses are evidences of disease that lend themselves well to preservation. I shall make no attempt to consider the numerous synonyms for and classifications of chronic proliferative joint disease of unknown etiology, but shall consider the conditions thus named collectively under the designation arthritis deformans. This disease, or something much like it, has been observed many times in various fossil vertebrates, as it has been also in wild and domestic animals. In the cave bear, it was common enough to have been endowed with the name, "cave gout" (goutte de cavernes, Hohlengicht).<sup>83</sup> Its occurrence in ancient skeletons of man is consistent with these facts.

Certain interesting but fragmentary skeletal remains found at Krapina, Croatia, have been referred to the Neandertal or Mousterian race. They seem to belong to the last interglacial period (Riss-Wurm), and in that case are early Neandertal. Some of the bones from Krapina, notably one lower jaw, show evidences of arthritis, which is called

<sup>80</sup> Means, H. J. *Am J Roentgenol* **13** 359, 1925.

<sup>81</sup> Hrdlička, A. *Bull Bur Am Ethnol* Washington, 1909, no 42, p 1.

<sup>82</sup> The early history of tuberculosis among the Indians is summarized in "Tuberculosis among the North American Indians," Report of a Committee of the National Tuberculosis Association, Senate Committee Print, Washington, 1923.

<sup>83</sup> Virchow, R. *Dermat Ztschr* **3** 4, 1896.

arthritis deformans The descriptions and plates <sup>84</sup> suggest that the process at the articulation of the mandible may have been an infectious arthritis, since a fistula is described as occurring below the joint and apparently pyorrhea, also, an ulna, two patellas and some vertebrae apparently show arthritis deformans Keith <sup>18</sup> stated that there is some "rheumatic change" in the form of lipping of the left tibia in the Rhodesian skeleton, which is of undetermined but probably ancient age, and belonged to a relative of the Neandertals The Neandertal skeletons are from 30,000 to 50,000, or more, years old

At the end of the glacial period in the reindeer period, in which men of modern skeletal type began to appear, there were also examples of arthritis deformans (from 15,000 to 30,000 years ago)

At Lyons, France, in 1925, Dr Lucien Mayet showed me an example of spinal arthritis deformans in a skeleton from Solutre, provisionally assigned to an Aulignacian level One of the Obercassel skeletons, believed to be Magdalenian, is described as having general arthritis deformans (arthritis ossificans) <sup>85</sup> The skeleton from Chancelade, in central France, excavated from a lower Magdalenian level, gives marked evidences of arthritis deformans (osteo-arthritis) about the head of the right humerus and scapula, according to the description of Testut, quoted by Ruffer <sup>86</sup>

Arthritis deformans was frequent in western Europe in the neolithic age and bronze age and in Roman times <sup>87</sup>

Egypt has furnished more examples of arthritis deformans <sup>88</sup> from ancient times than any other locality, and the recognition of this fact is owed to the admirable work of Wood-Jones From his investigations and from others, it seems that arthritis deformans was common in Egypt and Nubia, even in the archaic and predynastic periods, 4000 B C or earlier Ancient bones showing it date also from various dynasties, and from the occupation by the Greeks and the Romans, and from the time of the Copts, about 500 A D The disease is also common

84 Gorjanovic-Kramberger, Karl (footnote 47), Umschau **12** 623, 1908

85 Verworn, Bonnet and Steinmann (footnote 49, pp 10 and 192)

86 Ruffer (footnote 1, second reference, p 184), originally published as "A Pathological Specimen Dating from the Lower Miocene Period" Contributions à l'étude des vertèbres miocènes de l'Égypte, Cairo, Survey Department, 1917 In this article Ruffer gave a valuable review of cases of arthritis deformans from the neolithic, bronze and Roman periods in western Europe, with references to the literature

87 Rouillon A Lesions osseuses préhistorique de la Vendée, Angers, 1923, reviewed in Anthropologie, Paris **36** 153, 1926 Furst, Carl (footnote 5) Teissier and Roque, in Gilbeert and Carnot Nouveau traité de médecine, Paris, J B Baillière et fils, pt 8 p 121 Raymond, Paul (footnote 22) The two latter give other references to the literature

88 Bull Archeol Survey Nubia, 1908, no 2, has excellent illustrations

in Nubia at the present day. The British investigators believed that many lesions of bone ascribed by earlier scientists to tuberculosis and other diseases were in reality produced by arthritis deformans (Wood-Jones,<sup>13</sup> Smith,<sup>6</sup> Ruffer<sup>89</sup>)

Arthritis deformans in ancient bones from American Indians was described nearly fifty years ago (Landon<sup>15</sup> and Whitney,<sup>14</sup> in excellent, judicious articles) and has often been observed since in Indian remains from North and South America, especially in skeletons from Peru (Hrdlička<sup>16</sup> and MacCurdy<sup>17</sup>). It has been reported in other ancient bones from Patagonia by Lehmann-Nitsche<sup>90</sup>

The changes produced by arthritis deformans in earlier times do not seem to have been greatly different from those that one sees today, as far as one can determine from the numerous descriptions and illustrations that have been published. The spine (especially the lumbar spine) and the hip joint were the most common locations for it. Involvement of the knee joint was frequent. Other joints, such as the elbow, the shoulder, the sacro-iliac joint and that of the lower jaw, have also been found affected. The comparatively small number of reports of involvement of the fingers and the toes may be due to the ease with which these small bones may be lost or destroyed in old burial grounds, however, Wood-Jones observed several cases of it in the foot, hand and wrist. In old burial grounds, individual bones often cannot be identified as belonging to any particular skeleton. However, in a considerable number of cases, it could be shown that several or many joints in one skeleton were involved.

Bony union of adjacent articular surfaces (the proliferative type of Nichols and Richardson,<sup>91</sup> the atrophic type of some other authors) seems to have been comparatively rare (excepting, perhaps, the cases of Wood-Jones), while erosion, eburnation and deformity of the articular surfaces, with formation of bone in the capsule and ligaments (degenerative type of Nichols and Richardson, hypertrophic type of some other authors), was common. Immobility often resulted from the latter, especially in the spine. In the case of the spine, outgrowths from the edges of the bodies of the vertebrae, like irregular lips of bone, were common, as they are today, coalescence of such lips from adjacent vertebrae often produced immobility over larger or smaller portions of the spine. Many of the descriptions are not definite enough to let one determine the amount of ossification of the intervertebral

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<sup>89</sup> Ruffer, M. A., and Rietti, A. *J. Path. & Bact.* 1912, vol. 16. Ruffer (footnote 1, second reference)

<sup>90</sup> Lehmann-Nitsche. *La arthritis deformans de los antiguos Patagones*, *Rev. del Museo de la Plata* **11** 199, 1903. Verneau, R. *Les anciens Patagons*, Paris, 1903, reviewed by Moodie, R. L. *Ann. M. History* **10** 314, 1928.

<sup>91</sup> Nichols and Richardson. *Arthritis Deformans*, *J. M. Research* **21** (n.s. 16) 149, 1909.

disks, apparently such ossification was rare. Ruffer believed that irregularities occurring on the surfaces of bones at the point of attachment of muscles were due to ossification of the ends of tendons.

Ruffer studied sections of decalcified bones in some of his cases. He found the lesions superficial, the interior of the bone was normal, the bony thickenings were limited to the periosteum and neighboring tissues, the cartilage had atrophied, but signs of ossification of the cartilage were absent.

Smith (reported by Wood-Jones) observed in bones from Egypt a case of complete ankylosis of the spine, and there have been others like it. Almost all the skeletons of old persons from ancient Nubia showed spondylitis deformans. Smith and Dawson stated that rheumatoid arthritis "is par excellence the disease of the ancient Egyptians and Nubians." "The predynastic Nubian scarcely ever grew to adult life without experiencing some of its effects." Its manifestations were legion, of varied type and often of great severity. Ruffer<sup>1</sup> described many cases of it in bones from Egypt from various periods in its history, at great length and with meticulous care.

The most detailed account of arthritis deformans in the skeletal remains of American Indians is that of Hrdlička,<sup>16</sup> relating to the Peruvians. While the tibia and the humerus were sometimes involved, the spine and the hip joint were the commonest locations. He observed numerous cases of "mushroom head" femurs. There was sometimes considerable proliferation around the acetabulum, never synostosis.

Lehmann-Nitsche<sup>90</sup> found arthritis deformans present in about 4 per cent of ancient Patagonian skeletons. Rather curiously, the humerus and the elbow joint were somewhat more often affected than other parts. Apparently, the material came from between 100 and 150 skeletons. Contrary to his experience in the case of bones from Europe, he rarely found proliferations having the form of cauliflower in the bones from Patagonia. Polishing and ebullition were abundant. This he attributed to the fact that there was no rest for the damaged parts, owing to the nomadic life of these Indians.

It cannot be said that the study of arthritis deformans in the skeletal remains of ancient times throws any light on the causes of this calamitous disease, desirable as that would be. Race seems not to have had any influence. Negroes (Egypt), Indians, Caucasians of many nations, and even the Neandertal race all have been subject to it. All observers that mentioned the factor of age agreed that the bones indicated that adults, especially the elderly, were the persons affected. Several referred to the influence of exposure and moisture. Lehmann-Nitsche<sup>90</sup> alluded to the inclement climate of Patagonia, apparently in this connection. Gojanovic-Krambeiger<sup>84</sup> ascribed the "cave gout" of his specimens of the Neandertal race to the conditions of life in their cave dwellings. Wood-Jones<sup>13</sup> laid stress on the fact that the people along

the Nile spend much time dabbling in the water, and that they have probably always done so, furthermore, periods of cold weather may alternate with intense heat

Raymond<sup>22</sup> spoke of the frequency of arthritis in bones from caves, where moist conditions might be expected (In France, rock shelters and caves have been used as dwelling places from the time of the Neandertal or Mousterian race down to and including the present day) Ruffer<sup>89</sup> combated the theory that exposure to wet and cold operates as a cause of arthritis and implied that this theory is out of date, he reported on cases in skeletal remains of some of the driest and hottest places in the world, he made the valuable suggestion that if an equal number of remains of man from other regions than Egypt and from the same early periods were to be examined, arthritis might be found to be equally common in them Hrdlička<sup>16</sup> said of his Peruvian material that it showed plainly that the underlying cause was constitutional It is difficult to see how diet could have been a cause when peoples of such diverse habits were affected I do not know of any investigations that attempted to show how frequently arthritis was associated with diseases of the teeth in ancient times, such researches would be valuable though difficult on account of the rarity with which complete or nearly complete skeletons can be secured Bearing on this point, Keith<sup>48</sup> (who has had a large experience with skeletons of men of many races and from many periods) said that he had seen skeletons in which the teeth were affected and the joints sound, others in which the teeth were sound and the joints affected and others still in which both were affected Rather curiously, it seems to me, few of the observers quoted said anything of injury as a factor in producing arthritis, or spoke of the difficulty that exists in distinguishing the effects of arthritis deformans from those of some old fractures, particularly at the head of the femur Wood-Jones is one who did refer to this I have met the difficulty in specimens from the dissecting room, when they were unaccompanied by histories of the cases

*Tumors*—Tumors produce such striking alterations in the forms of bones that a collector could not overlook them One would, then, expect many reports on tumors of bone of ancient times, but the contrary is the case, there are few such reports I have not been able to learn of any cases in bones older than those from Egypt, which I shall mention

*Osteoma* Small bony tumors are fairly common in the skulls of ancient Peruvians, most often in the upper surface Osteomas or exostoses of the external auditory canal were mentioned by Whitney<sup>14</sup> as occurring in the skulls of Indians from all parts of the United States from Canada from Mexico and especially from Peru He stated that the meatus might be entirely closed, and suggested a connection with the pressure on the posterior part of the skull that is

known to lead to flattening. Such exostoses are not an extreme rarity in patients of today. These bony growths about the ear in old skeletons have been described briefly by Hrdlička,<sup>11</sup> who has assembled a fine collection at the National Museum, Washington. He said, "These are generally hard osteomata, from one to three in number, just within the orifice of the osseous meatus. They were in no case seen to coalesce, and though they may almost close the meatus they were never seen to do this entirely. They were generally bilateral. Of 278 skulls, nineteen showed these exostoses, the specimens coming from the Chicama valley, Peru." Wood-Jones<sup>12</sup> referred to a case of the same kind from Nubia of the early Christian period. Moodie<sup>13</sup> reviewed other bone tumors collected by Hrdlička in Peru, and now housed in the museum at San Diego, Calif. He thought one or more of these tumors might be examples of meningioma or dual endothelioma invading the skull and provoking external hyperostosis.

**Osteosarcoma.** MacCurdy<sup>14</sup> described and gave a fine illustration of a large osteosarcoma of the cranium. Smith and Dawson<sup>6</sup> mentioned a large osteosarcoma of the femur and gave a good photograph of it. They also mentioned two of the end of the humerus. These were in skeletons from the cemetery near the Pyramids of Gizeh, dating from the fifth dynasty, and apparently were the most ancient examples of malignant tumors then recorded. Ruffer<sup>15</sup> described a large tumor, probably osteosarcoma, of the innominate bone, from Egypt, of about 200 to 300 A.D. It was impossible to tell whether this tumor was primary or secondary.

**Carcinoma.** Smith and Dawson<sup>6</sup> said of Egypt that "no evidences of true cancer occur until comparatively recent (Byzantine) times, when cases of malignant disease involving the base of the skull and sacrum suggest the presence of epithelioma of the naso-pharynx and rectum, respectively." Representations of tumors in human figures left by the ancient Greeks and Peruvians are referred to briefly on an ensuing page.

#### OBSERVATIONS ON ANCIENT TEETH

Ancient skulls have usually suffered a postmortem loss of teeth, and that is a serious obstacle to studies in this department. Anomalies, malformations and mutilations must be omitted from consideration in this article, which will limit itself to inflammatory and destructive diseases of the teeth and those of the jaws due to diseases of the teeth. Grinding down of the teeth (abrasion, attrition) produced by coarse and gritty food was frequent and often extreme in ancient races, exposure and infection of the pulp are said to have been common.

92 Moodie, R. L. Tumors of the Head among Pre-Columbian Peruvians, *Ann. M. History* 8: 397, 1926.

93 Ruffer (footnote 1, second reference) *J. Path. & Bact.* 18: 480, 1914.

The earliest known human jaws, the Piltdown jaw, which some comparative anatomists regard as that of an ape, and the Heidelberg jaw, exhibit some abrasion of the teeth but not any other disease

*Neandertal Teeth*—The roots of some specimens of teeth of Neandertal man are stout, and in the case of the molars and premolars the roots are fused (taurodont-Keith or prismatic-Kramberger) Fragments of several jaws belonging to this race at Krapina, in Croatia, were described by Gorjanovic-Kramberger<sup>84</sup> One of these has already been mentioned as showing evidence of arthritis and a fistula Some of the teeth of this jaw were covered with tartar and the margin of the alveolar process presented a fine punctate appearance From the description and the illustration, I should infer that there had been pyorrhea alveolaris (periodontoclasia) Pointlike depressions on some teeth may have resulted from caries (probably not), these appear to have been defects in the enamel These bones are usually rated as rather early specimens of the Neandertal race, as is the lower jaw from Ehringsdorf, near Weimar, Germany, described by Virchow<sup>94</sup> The latter specimen presents the results of a purulent process at the alveolar margin, the teeth are well worn and where the neighborhood of the pulp cavity has been reached "compensatory" (secondary) dentine has formed

The skull of La Chapelle aux Saints in the Dordogne region, France, that of an elderly person, in which dental lesions were detected and described by Baudouin,<sup>95</sup> had lost many teeth during life, the jaws gave evidences of pyorrhea alveolaris ("gingivite expulsive" or "polyarthrite alveolaire"), but not any trace of caries of the teeth

Still another Neandertal skull, that of LaQuina, discovered by Henri Martin, belonging to a younger person, showed, according to Baudouin, deposits of tartar, especially on the molar teeth, and evidences of gingivitis between the molars, which he attributed to the use of toothpicks, dental caries was not present

These instances are the only allusions to diseases of the teeth of the Neandertal race that I have seen As far as these few specimens are concerned, pyorrhea alveolaris was common, tartar not rare, and dental caries unknown However, in the case of several of the skulls of this race, I have not met with any reference to the presence or absence of disease of the teeth and jaw

Martin<sup>96</sup> thought that the Neandertalers were carnivorous, Boule<sup>96</sup> that their diet was mixed Roots, nuts, fruits and berries, it seems, would have been the most available forms of vegetable food for such a

94 Virchow, Hans Die Unterkiefer von Ehringsdorf, etc, Ztschr f Ethnol 47 447, 1915

95 Baudouin, M Sem med 32 170, 1912

96 Martin, reviewed by Boule Anthropologie 33 387, 1923

savage people. Probably the diet varied with differing times and places. It is likely that the habits of those who dwelt in the center of Europe during the warm Riss-Wurm interglacial period differed from the habits of the hunters of the cave bear in the high Alps. Charcoal found mingled with their implements indicates that this race used fire, whether or not they cooked their food must remain a matter of conjecture.

The Rhodesian skull from South Africa, generally regarded as related to the Neanderthal type, of undeterminable but probably ancient date, has teeth that are well worn and that show marked caries and alveolar abscesses.<sup>97</sup>

*Late-Paleolithic Teeth*—For the condition of the teeth in the late paleolithic or reindeer period, I have been able to find only a few notes. The jaws of the Old Man of Cro-Magnon (Aurignacian) indicate that he suffered from pyorrhea, as well as from bone cysts (MacCurdy<sup>98</sup>).

The specimen generally called the Chancelade skull (Magdalenien), now in the museum at Périgueux, southwestern France, had lost the teeth of the upper jaw during life, presumably from disease. One of the Obercassel skeletons (Magdalenien) had a fistula of the lower jaw<sup>49</sup> and the remains of purulent inflammation of the periodontal membrane of a right molar, but not any caries. The teeth were well worn.

The only reference to dental caries occurring at this early period that I have seen is that of von Lenhossek,<sup>98</sup> who observed it in a brachycephalic skull from Nagysáp, Hungary, of the end of the diluvium. Von Lenhossek made the interesting suggestion that dental caries may be regarded as an epidemic disease, comparable to cholera and pest, which was brought into Europe from Asia by a brachycephalic race that invaded Europe just prior to the neolithic period.

At the meeting of the American Association for the Advancement of Science, in December, 1928, Fay Cooper Cole described two skeletons having root abscesses, loss of teeth during life and absorption of the alveoli. These skeletons were from shell heaps in Algeria, excavated by an expedition from Beloit College (U. S. A.), and the nature of the implements found with them indicates that they belonged to a period corresponding to the Aurignacian of France. To which level they may be properly referred cannot be fully established at present.

*Neolithic and Later Teeth (Europe)*—Baudouin<sup>95</sup> said that an authentic case of dental caries has not been shown in skeletal remains from any time prior to the neolithic period. With the introduction of agriculture, polished stone tools and what he calls civilization in general, dental caries appeared, although it was still ten times less

<sup>97</sup> MacCurdy (footnote 8, vol. 1, p. 370), Keith (footnote 48, p. 398).

<sup>98</sup> Von Lenhossek, M. Die Zahnkaries Einst und Jetzt, Arch. f. Anthrop.



frequent than at present. Substantially the same opinions were advanced in articles by Baudouin,<sup>99</sup> Rouillon and Baudouin<sup>100</sup> and Bouvet<sup>101</sup>

Ruffer<sup>102</sup> reviewed the evidences of disease of the teeth in ancient Europe with numerous references to the literature. He alluded to skulls from a time apparently earlier than the neolithic period as having carious teeth. He concluded that, in the neolithic period itself in France, caries was neither common nor severe. Ruffer also commented on the occurrence of dental caries in England from the neolithic to the Anglo-Saxon period. Whether or not caries increased during the later periods is not clear (in general, it was found in about 20 per cent of the skulls). Keith<sup>103</sup> referred to a small group of neolithic skulls in Coldrum, England, as not having dental caries. Tratman,<sup>104</sup> describing a small series of teeth from a neolithic site in England, found that fifty-five of 100 teeth showed chronic periodontitis. There was a number of specimens that showed caries. Furst<sup>5</sup> found carious teeth not rare in skeletal remains in Scandinavia (apparently of the neolithic period).

One of the first to make a survey of the teeth in a considerable number of ancient skulls was Mummery<sup>105</sup>. His work has been quoted by many subsequent writers. Mummery found, among skulls excavated in England, dental caries in two (2.94 per cent) of sixty-eight neolithic skulls (dolichocephalic), in seven (21.87 per cent) of thirty-two skulls of the bronze age, in twenty-four (40.67 per cent) of fifty-nine Yorkshire early dolichocephalic skulls, in nine (20.45 per cent) of forty-four ancient miscellaneous skulls, in forty-one (28.67 per cent) of 143 skulls of the Roman period, and in twelve (15.78 per cent) of seventy-six Anglo-Saxon skulls.

Von Lenhossek criticized Mummery's work, saying that it did not take account of teeth lost during life, such loss, he said, is chiefly due to caries. Apparently, von Lenhossek laid much less stress on pyorrhea alveolaris (periodontoclasia) and on dental abscess due to abrasion as causes of loss of teeth than did the British and American observers reviewed in this article. His own conclusions were based on the examination of more than 1,000 skulls in Budapest. It should be under-

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99 Baudouin, M. *Sem. dentaire* **5** 444, 1923, reviewed, *Am J Phys Anthropol* **8** 342, 1925.

100 Rouillon and Baudouin. *Presse Dentaire* **26** 440, 1924, Rouillon (footnote 87).

101 Bouvet, reviewed *Anthropologie* **34** 306, 1924.

102 Ruffer, M. A. *Study of Abnormalities and Pathology of Ancient Egyptian Teeth*. *Am J Phys Anthropol* **3** 335, 1920, reprinted (footnote 1).

103 Keith (footnote 48 p. 13).

104 Tratman, reviewed by Moodie (footnote 52, p. 330).

105 Mummery, J. R. *The Relation of Dental Caries in the Ancient Inhabitants of Great Britain and Aboriginal Races, to Food and Social Conditions*, *T-Odontol Soc Great Britain* **2** 7, 1870.

stood that jaws showing loss of teeth during life were counted by him as having caries. Von Lenhossek<sup>98</sup> found the frequency of caries increasing slightly from early to later periods in central Europe, as shown by skeletal remains, 85 per cent of the skulls from the Roman period first century, and 83 per cent of those from the same period, fourth century, showing caries, as compared with 86 per cent of thirteenth century skulls, and 90 per cent of recent skulls. Schweiz<sup>106</sup> said that, according to the opinions of most writers, caries of the teeth is favored by culture and is comparatively rare under natural conditions. He examined the teeth of Alemannian Germans of about the tenth century. In 7,000 teeth, about 7 per cent were carious and tartar was frequent.

*Ancient Egyptian and Nubian Teeth*—The most extensive reports on the teeth of ancient Egyptians and Nubians are those of Wood-Jones<sup>1</sup> Smith,<sup>13</sup> Smith and Dawson<sup>6</sup> and Ruffer<sup>102</sup>. One who entered the same field early, as has been stated, was Mummery<sup>105</sup>. Thoma,<sup>107</sup> who studied the material in the Peabody Museum, Cambridge, Mass., found caries uncommon in skulls from ancient Egypt. Thoma encountered some bone abscesses.

Wearing or grinding down or attrition or abrasion of the teeth of Nubians from food that was coarse or contained much grit or sand was described by all the first three writers named. Such wearing away of the teeth was most marked in predynastic times and among the poorer people in later periods. Teeth were often worn down so as to expose the pulp cavities, and the frequent alveolar abscesses seen in such cases, as well as most of the dental disease seen in the archaic Egyptians and the poorer classes of the ancient Nubians, were attributed by Smith<sup>13</sup> to infection of the pulp. Wood-Jones described some severe alveolar abscesses with much destruction of bone.

Ruffer found evidence of the existence of pyorrhea in predynastic times and at later periods in Egypt and Nubia. He saw it in skulls of the twenty-fifth and twenty-sixth dynasties (from 750 to 500 B.C.) and in skulls of Copts of about 400 to 500 A.D. He saw it often among modern Egyptians. Ruffer regarded pyorrhea as the principal cause of the loss of teeth, and as a more common cause of alveolar abscesses than attrition, some such abscesses were caused by the decay of teeth.

Dental caries was rare in predynastic times, according to Wood-Jones,<sup>13</sup> it was more common during the New Empire, there were many examples in the Ptolemaic period, but it first became really common in the Byzantine period. Smith<sup>13</sup> also said that dental caries was exceedingly rare among the predynastic people, and that among the

106 Schweiz Arch f Anthropol **15** 41, 1917

107 Thoma, K. H. Oral Diseases in Ancient Nations and Tribes, J. Allied Dental Soc. New York **12** 327, 1917

poorer classes it never became common until modern times. But the ancient Egyptians of the wealthy classes who acquired habits of luxury suffered much from it. He mentioned that, in more than 500 skeletons of aristocrats of the time of the pyramid builders, formation of tartar, dental caries and alveolar abscesses were at least as common as they are in modern Europe. Ruffer seemed not to be certain that dental caries was less frequent in ancient times than it became later, but the facts cited by him indicate that such was the case. Ruffer apparently leaned toward the conclusion that there was some relation between diseases of the teeth and arthritis deformans, but he was cautious in expressing any definite opinion.

The observers mentioned agreed that evidence for the Egyptians ever filling cavities of teeth with gold or with anything else is lacking. In the rare examples of gold about the teeth, the gold was intended to be ornamental rather than useful. Nor did they find anything to indicate that extraction was practiced, or any other operative measure. Ruffer said also that there was nothing to point to the use of the toothbrush (which he characterized as an "instrument of torture").

Hooton<sup>108</sup> described a mandible from a tomb at Gizeh, of the Old Empire, in which an abscess had formed about the roots of the right first molar, the tooth being much worn and the pulp exposed. Two holes about 2.5 mm. in diameter led from the buccal surface of the jaw into the abscess cavity. They seemed to have been drilled and their nature was recognized by Thoma and Blumenthal. Todd<sup>109</sup> thought that the foramina in this specimen may have been natural and not produced by an operation.

*Ancient Indian Teeth of North and South America*—Although American museums contain an immense amount of material that might give valuable information, the number of published articles on the teeth of the ancient Indians is not large. Hrdlička<sup>110</sup> described a morphologic peculiarity of the upper incisors of the Indians that is present in a large majority of persons of this race, and is seen to a smaller extent in other yellow-brown races. It depends on a hollow on the lingual surface making these incisors "shovel-shaped."

Hrdlička<sup>111</sup> found that dental caries occurred but rarely in skulls from Peru. He gave figures for 160 lower jaws from the Chicama Valley of 708 teeth, 16 were carious. The absent teeth had been,

108 Hooton, E. A. *Harvard University African Studies. I. Oral Surgery in Egypt during the Old Empire*, Cambridge, Harvard University Press, 1917, p. 29 (with good plates).

109 Todd, T. W. *Egyptian Medicine, A Critical Study of Recent Claims*, *Am Anthropol.* **23**: 460, 1921.

110 Hrdlička, A. *Am J Phys Anthropol.* **3**: 467, 1920.

111 Hrdlička (footnote 16 p. 61).

for the most part, lost post mortem MacCurdy,<sup>112</sup> in his studies on skeletal material from the highlands of Peru, found considerable dental disease, without evidence of any effort to treat such disease Of 131 skulls, more than two thirds had decayed teeth Of 1,259 teeth present, 194 (15.4 per cent) were decayed The chief cause of the loss of teeth, aside from caries, seemed to him to have been pyorrhea alveolaris, which affected more than 13 per cent of all these jaws Alveolar abscess was present in twenty-two cases, bone cyst in about ten, caries of the jaw in six and marked formation of tartar in thirteen Moodie<sup>113</sup> recently began systematic studies on the diseases of ancient teeth from Peru He has found pyorrhea prevalent, and has found that it resulted in an absorptive alveolar osteitis causing an appalling loss of teeth He has thus far seen little evidence of a prevalence of caries Thoma<sup>107</sup> described briefly alveolar abscesses and malformations of the teeth of Peruvians

Hrdlička,<sup>114</sup> in a report on skeletal remains from Arkansas and Louisiana, said that decayed teeth, though not common, were fairly frequent sixteen skulls did not show any teeth decayed or lost during life, thirty-nine had one or more decayed or lost during life A good study was that of Leigh,<sup>115</sup> which should be read Leigh chose skulls from four tribes of Indians, usually prehistoric, but at least living under natural conditions, free from the influence of white men In sixty-eight skulls of Kentucky Algonquins, a sedentary people living on maize, and by hunting and fishing, he found marked attrition of the teeth, many alveolar abscesses, a little caries (twenty-eight lesions in 30 per cent of the specimens examined), some abscesses resulting from exposure of the pulp, periapical bone lesions (in 40 per cent) but not much periodontoclasia, which was chiefly senile, and comparatively rare calculi In ninety-two skulls of the Sioux, buffalo hunters, eating fruit and vegetables to a limited extent, he found the least attrition of any and little caries (slight lesions in ten of the ninety-two), alveolar abscesses (in 16 per cent) mostly from exposure of the pulp, and not much periodontoclasia (in 13 per cent) The teeth were clean In 129 skulls of Arikara (a branch of the Sioux), mainly sedentary, living on maize pounded in stone mortars and by some hunting of the buffalo, he found much attrition, many alveolar abscesses, considerable caries (eighty-six lesions in 28 per cent of the skulls), alveolar abscesses (in 35 per cent), mostly from exposure of the pulp, and periodontoclasia (in 33 per cent) The teeth were dirty One skull presented arthritis

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112 MacCurdy (footnote 17, p. 276)

113 Moodie, R. L. Studies in Paleodontology, *J. Am. Dent. A.* **15** 1826, 1928

114 Hrdlička, A. *J. Acad. Nat. Sc. Philadelphia* **14** 210, 1909

115 Leigh, R. W. Dental Pathology of Indian Tribes of Varied Environmental and Food Conditions, *Am. J. Phys. Anthropol.* **8** 179, 1925

of the temporomandibular joint In 113 skulls of Zuni, a sedentary people, more advanced in cultural development than most tribes, living chiefly by planting, especially of maize, and a little hunting, he found moderate attrition of the teeth, caries (in 75 per cent), commonly accretions, much early loss of teeth, alveolar abscesses in 52 per cent, and periodontoclasia (in 56 per cent) There was more exposure of the pulp from caries than from abrasion The teeth were dirty from calculi and stain

As a further example of the fact that dental disease was not always rare among the Indians, I may mention material from a village site at Westfield, N Y, pronounced by Arthur Parker to be early Iroquois (Erie)<sup>116</sup> These were a sedentary people, probably living largely on maize The skulls were badly preserved and many teeth had dropped out Sixty-six teeth present in the jaws were free from caries, ten showed caries, 103 loose teeth were free from caries and fifteen had caries The cavities were large and the disease advanced The teeth were nearly all those of adults Many loose teeth showed marked thickening and even fusion of the roots in molars and bicuspid, these were not usually the carious ones Sections of one such tooth showed the root thickening to be due to a new formation having the structure of cancellous bone, the root canal contained a large mass of secondary dentine The root thickening was evidently caused by periodontal inflammation

The factors making for sound or unsound teeth, including the diet and the asserted influence of coarse food in cleaning the teeth, and the reported low incidence of dental caries among the Eskimos, who live on a diet of meat and fish, urgently call for further investigation, as does the possible influence of racial constitution These studies are, however, outside the scope of this review<sup>117</sup>

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<sup>116</sup> I am indebted to R P Wright, of Erie, Pa, for an opportunity to see the specimens

<sup>117</sup> The following additional references give valuable information Ritchie, S G Rep Canadian Arctic Expedition, 1913-1918, abstr, *Am J Phys Anthropol* 8 343, 1925 Leigh, R W Dental Pathology of the Eskimo, abstr, *Am J Phys Anthropol* 9 400, 1926 Hellman, M Food and Teeth, *Dental Cosmos*, 1925, vol 67, abstr, *Am J Phys Anthropol* 9 398, 1926 Chappel, H G Jaw and Teeth of the Ancient Hawaiians, abstr, *Am J Phys Anthropol* 11 140, 1927 Black, D Human Skeletal Remains, etc, *Geol Survey China*, abstr, *Ann M History* 8 328, 1925 Gillett, H W Contacts Between Archeology and Dental Research, *Am Anthropol* 29 291, 1927 Dental Caries and Race, abstr, *Am J Phys Anthropol* 7 405, 1924 Dr W D Strong of the Field Museum, Chicago (in a personal communication to me), has compared the teeth in about forty Eskimo skulls, dating from about 1890 or earlier, with those in a series of 250 living Eskimos, all from northern Labrador The amount of dental caries and loss of teeth was strikingly greater in the living Eskimos There has probably been a gradual increase in the proportion of food of the kind used by the white race during the later period These cases are now being studied and the results will be published later

The practice of inlaying the teeth with jadeite, turquoise and the like for the purpose of ornament (not in treatment for disease) among the Mayas of Mexico and Central America and among the Indians of Ecuador was described by Van Rippen,<sup>118</sup> who gave a valuable review of ancient attempts at dental surgery

#### OBSERVATIONS ON MUMMIES AND DRIED BODIES

The first published account treating of the study by modern methods of the anatomy and the histologic structure of the soft parts of ancient dried bodies was, so far as I can learn, that of Wilder.<sup>119</sup> Many more mummies have been destroyed or have been scraped so as to reveal the bony skeleton than have been saved for examination of the soft parts. Ruffer justly lamented this fact for Egyptian mummies. I suspect that it is equally true for those of Peru, of our southwestern states and of other regions, although the Egyptian material has been far more abundant. Smith and Dawson<sup>6</sup> gave vivid descriptions of the evidences of ancient tragedies in Egypt in the mummy of King Seknenrê, with its matted hair, wounds of the head and face and bones broken and cut by axe and spear, and in the body of a 16 year old girl, six months pregnant, whose wrists had been broken while she was defending herself from blows, one of which fractured her skull, the assailants presumably having been her own relatives. While the possibilities of such examinations are strictly limited, further study will surely bring to light valuable information. It is not unreasonable to expect that eggs of parasitic worms may be found in intestinal contents. Trichinosis might be detected in the mummified cats of Egypt, as well as in human bodies. While not much is to be hoped for in examinations for pathogenic bacteria, it seems to me not improbable that tubercle bacilli might be discovered in a body that had been rapidly dried, even after the lapse of thousands of years.

The Egyptian mummy, according to Smith and Dawson,<sup>6</sup> was usually prepared by removing the brain through the nose and by removing the abdominal and thoracic viscera, but not the heart, through an abdominal incision. The viscera were placed in "canopic jars" or, after being soaked in brine, were wrapped in cloths, with gums and sawdust, and little images of the gods, to be returned to the body later. The body was soaked in brine for seventy days, according to Herodotus, but for only half that time, according to Smith and Dawson, after which it was wrapped in linen bandages. The body cavity was filled with cloths, mud, sawdust and miscellaneous rubbish. Other details such

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118 Van Rippen. *Dental Cosmos* 59 861, 1917

119 Wilder, H. H. *The Restoration of Dried Tissues, with Especial Reference to Human Remains*. *Am Anthropol N S* 6 1 1904

as the use of artificial eyes and the external ornamentation, varied greatly at different periods, as did the addition of resins and other preservatives.

Peruvian mummies were sometimes eviscerated, but usually not. The body was bandaged, sometimes in a sitting posture with the knees flexed, sometimes extended. How much was done in the way of intentional embalming is not known. Balsam of Peru may have been applied to the bandages, which were of cotton. Apparently, the principal factor in the preservation of all mummies was a dry climate. Wood-Jones<sup>119</sup> found bodies from the predynastic period in Egypt (at least 5,500 years old), when artificial mummification was not practiced, which showed muscles and tendons, the skin and the hair, the nails and the eye and even the convolutions of the brain in good preservation. Mummies from Arizona and New Mexico in this country are merely dried bodies which the arid climate of the states has preserved. I do not know of any published accounts of examinations of Alaskan mummies, some specimens are now being studied at the American Museum of Natural History, New York, by Shapiro. Mummification in America and Australia was also described by Dawson.<sup>119a</sup>

*Technic of Gross Examination of Mummies and Dried Bodies*—Wilder,<sup>120</sup> using material from Peru and from Utah in the United States, let the tissues swell for from twelve to forty-eight hours in a 1 to 3 per cent solution of potassium hydroxide, until they reached nearly their normal volume, then placed them in water, watching carefully that too much further swelling should not occur, and finally placed them in a 3 per cent solution of formaldehyde. In my laboratory, using similar material, my associates and I have found that merely soaking in a weak solution of formaldehyde (from 1 to 2 per cent) permits a satisfactory dissection. Ruffer,<sup>120</sup> working on Egyptian mummies, seems to have preferred, for dissection, carbonate of soda 2, solution of formaldehyde 0.5 and water 97. The part to be dissected was immersed in this solution for twenty-four hours or more. By any method, the fluid acquires a brownish-yellow color from the tissue.

Of course, everything depends on the completeness of the body and the state of preservation. It may be badly eaten by insects and worms. All observers agree that, in favorable cases, the muscles, the tendons, the large arteries, the veins and the nerves may be identified without much difficulty, and sometimes the cartilages of the larynx, trachea and bronchi, and the aorta. The condition of the great viscera of the thorax and of the abdomen varies greatly, but is usually much less satisfactory than that of the parts just enumerated, in the bodies of American Indians, the viscera may be dried to the consistency of thin mem-

119a Dawson, J. Royal Anthropol Inst Great Britain & Ireland **58** 115, 1928.

120 Ruffer, M. A. Note on the Histology of Egyptian Mummies, Brit M J, 1909, pt 1, p 1005. Remarks on the Histology and Pathology of Egyptian Mummies, Cairo Sc J **4** 1, 1910, Histological Studies on Egyptian Mummies. Mem pres a l'Inst Égyptien, 1911, vol 6, On Arterial Lesions Found in Egyptian Mummies, J Path & Bact **15** 453, 1911, Pathological Notes on the Royal Mummies. Mitt z Gesch d Med u d Naturw, 1914, vol 13. These are the most important of Ruffer's numerous papers on mummies. All of them are reprinted in Ruffer (footnote 1 second reference).

branes In Egyptian mummies, the viscera were largely removed during the preparation of the body, and the embalmers were apt to damage the aorta The heart is found much shrunken and apt to crumble, however, its valves are sometimes recognizable The brain in predynastic Egyptian bodies is sometimes found dried into a small, hard mass, giving, in miniature, the convolutions and the sulci The eye is sometimes preserved, including the pupil The hair, a resistant tissue, is usually well preserved, finger and toe nails often are Wilder<sup>110</sup> noted that the ridges and folds of the skin of the hands and feet may be preserved In the body of a baby Basket-Maker<sup>111</sup> that I have seen, prints from the foot and toes could easily have been made Tattooing may show distinctly, as it did in the mummies of dancing girls (eleventh dynasty) tattooed with a pattern identical with that shown on faience figures of dancing girls belonging to about the same period<sup>111</sup> Exceptionally, such organs as the appendix, the cervix uteri, the thyroid gland, the papillae of the tongue, the ureter and the suprarenal gland have been recognizable Smith and Dawson<sup>6</sup> told of the mummy of a woman, having the large breasts of lactation, buried along with her baby Ulcers and wounds have been seen on Egyptian mummies, but it may be impossible to distinguish between antemortem wounds and the hacking of the body done in ancient times by grave robbers

*Technic of Histologic Examination*—By far the largest amount of work was done by Ruffer<sup>120</sup> He placed the tissue in a preparation made of alcohol 30, water 50, and a 5 per cent solution of carbonate of soda 20, he sometimes used 1 per cent formaldehyde instead of alcohol and water Fixation was completed in alcohol He embedded the tissue in paraffin, and said that he obtained good sections, staining with hematoxylin and eosin, or with various aniline dyes

In my laboratory, my associates and I have used fixation in formaldehyde, 1 to 2 per cent without any alkali, hoping to avoid damage to the finer structures This may have been a mistake, for the tissues remained so hard that we could not make sections after embedding them in paraffin, usable sections were secured on embedding the tissue in celloidin Wilder<sup>110</sup> and Wilson<sup>122</sup> have also worked on American mummy material In general, the Egyptian mummies seem to have the structures of the large viscera better preserved than has been found to be the case in dried American bodies, as a rule, and the Egyptian mummies have given better results with nuclear stains The failure of Egyptian mummies to show red corpuscles may be due to the soaking of the body in brine, the rapid drying of the American bodies probably made preservation of red corpuscles possible The technic for preparing sections of bone has been discussed in connection with the diseases of bones

*Histology of Mummies and Dried Bodies*—All observers agree that the structure of common connective tissue, adipose tissue and cartilage is usually well preserved Elastic tissue may or may not take specific stains The cross striae of skeletal muscle fibers have been found both in Egyptian mummies and in American mummies, they may be seen well in teased preparations (fig 11) Ruffer was successful in showing striations in heart muscle The connective tissue framework of

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121 The Basket-Maker Indians preceded the builders of pueblos, their remains must have an antiquity of many centuries

121a Winlock Bull Metropolitan Museum of Art, New York, 1923, pt 2, p 26

122 Wilson, G E A Study in American Paleohistology, Am Naturalist **61** 555, 1927





Fig 11—Skeletal muscle fibers showing cross striations from a Peruvian mummy, reprinted from H U Williams (Arch Path 4 26 [July] 1927)



Fig 12—What are believed to be red corpuscles from a hemorrhage into the muscles of a Peruvian mummy, reprinted from H U Williams (Arch Path 4 26 [Jul] 1927)

nerves may be all that remains, but Ruffer sometimes could demonstrate the medullary sheaths and even remnants of axis cylinders. As far as I can learn, it has not been possible to identify red corpuscles in Egyptian mummies. My associates and I found what we believe to be red corpuscles in the tissues of a Peruvian mummy (fig 12). About six months later Wilson reported finding them in Basket-Maker, Pueblo and Peruvian mummies. Rather curiously, the blood cells measured in my laboratory were sometimes larger than normal red corpuscles, being 8 or even 9 microns in diameter, while Wilson's cells averaged only 19 microns.

The blood vessels are usually well preserved, and the layers of their walls may be plainly made out, but the intima is not likely to be in good condition.

Ruffer was sometimes able to demonstrate the alveolar structure of the lungs, though the finer details were wanting. In the few American bodies that have been studied, the lungs were collapsed.

The liver cells have, as a rule, been found poorly preserved, the general arrangement that is characteristic of liver is about all that can be shown.

Little work has been done on the stomach and intestines, and that chiefly by Ruffer<sup>10</sup>. The layers of the walls may be recognizable, but the epithelium is wanting.

The only work on the kidneys that I know of was that of Ruffer, who was able to secure sections that showed the cortex, medulla, tubules and glomeruli, but not the finer details of these structures, even with high magnification.

Wilson<sup>11</sup> examined a thyroid gland from a Basket-Maker body. Only the connective tissue framework remained and epithelium was not present. Ruffer<sup>10</sup> had about the same result with testicles and mammary glands.

The epidermis is sometimes well preserved and sometimes wholly missing. Ruffer secured some excellent sections showing epidermis and even sweat glands. Simandl<sup>12a</sup> has published photographs of skin and cross-striated muscle from an Egyptian mummy. I have recently obtained good sections from the skin of the foot of a Basket-Maker baby from Arizona. These sections took some nuclear stain (fig 13). Nuclei, in general, do not stain, although Ruffer had some success in demonstrating them, his attempts seem not to have yielded important results. Bacteria and mold fungi have often been observed in mummies and dried bodies. Ruffer was able to stain gram-positive and gram-negative organisms and spores. The certain occurrence of much putrefaction in these bodies makes it nearly impossible to connect such bacteria as may be seen with any disease process. But it seems to me that there is a good chance that tubercle bacilli and lepra bacilli may yet be found.

*Serologic Tests*—The results reported from attempts to secure precipitin and anaphylactic reactions have been somewhat contradictory, with the weight of the evidence indicating negative results. The majority of these tests have been made on Egyptian mummies that had presumably undergone the prolonged soaking in brine. It would be worth while to make more tests on bodies that have only been dried, taking material that might be expected to contain plenty of dried blood or serum. A brief reference to such tests will be found in my article on Peruvian mummies<sup>12b</sup>. If blood corpuscles could be obtained in sufficient quantities agglutination by serums of the various blood groups might be tried.

122a Simandl. *Anthropologie*, Prague 6 56, 1928.

123 Williams, H. U. *Gross and Microscopic Anatomy of Two Peruvian Mummies*, *Arch Path* 4 26 (July) 1927.

*Moorleichen or Bog Bodies*—Something like mummification has been described in the case of the brown-stained, much flattened bodies known as "Moorleichen" that have been exhumed from sphagnum bogs in Schleswig-Holstein and other parts of northern Germany Aichel<sup>124</sup> stated in his review that more than fifty such bodies had been recovered As far as they can be dated, they belong to around 200 to 300 A D

*Histology of Moorleichen or Bog Bodies*—The degree of preservation varied much in different cases Wounds of the body were often visible The acid swamp water had led to decalcification of the bones and solution of the muscles, while hair, nails, cartilage and connective tissue were often well preserved The brain was sometimes recognizable as a brown mass containing cholesterol The condition of the other viscera varied In a female child described by Aichel, the fascia, vessels, tendons and nerves of the extremities were recognizable, also the liver, gallbladder, stomach and part of the intestine and the papillae of the tongue The Moorleichen rarely revealed traces of cells Collagen showed up well and



Fig 13—Low power magnification of a section of the skin from the sole of the foot of the dried body of a Basket-Maker baby about 10 months old The Basket-Maker antedated the builders of the pueblos in New Mexico and Arizona, so that the body must have been many centuries old, no exact date can be fixed Drs Hooton, Kidder and Guernsey supplied me with the specimen

outlined many structures, elastic tissue was not preserved, blood vessels contained masses that were probably blood corpuscles, the structure of medullated nerves was complete, except that axis cylinders were wanting, muscular tissue was missing, cartilage was in good condition, the bones were largely decalcified, but the minute structures were plainly visible, even to the bone corpuscles Liver cells were not distinguishable, in the glands of the stomach, the epithelium was, in part, preserved The tissues had suffered from the boring into them of the roots of plants, which had even made holes of fairly large size in the bones

*Pathologic Changes in Mummies, Dried Bodies and Moorleichen*—(The evidences of disease of the bones and the teeth have already been considered ) All the authorities that I have cited as having worked on

<sup>124</sup> Aichel, Otto Ueber Moorleichen, *Anthrop Anz* 4 57, 1927 (with complete bibliography)

Egyptian mummies refer to calcifications or arteriosclerosis of the aorta and arteries. The principal types of arteriosclerosis seem to have been represented, as far as can be determined from the larger arteries. The disease was certainly not rare, and it occurred at various periods. Shattock<sup>125</sup> was apparently the first to report making sections of a sclerotic and calcified aorta. I have described thickening of the intima with calcification and an adherent thrombus in the posterior tibial artery of a Peruvian mummy<sup>126</sup> (fig. 14).

Wilder<sup>119</sup> mentioned carbonization of the lungs in Basket-Maker bodies. In a Basket-Maker baby (about 10 months old) being studied at the time of writing in my laboratory, the collapsed lung tissue already shows quantities of opaque granules that must, for the most part, rep-



Fig. 14—Posterior tibial artery from a Peruvian mummy, showing a slight thickening of the intima with calcification, and a calcified thrombus, nitrate of silver and eosin stain, reprinted from H. U. Williams (*Arch. Path.* 4:26 [July] 1927).

resent extraneous material that was inhaled during life. At the present time, the impalpable dust of the floors of the shelters where such bodies are exhumed is so easily stirred up as to impregnate the atmosphere, becoming a serious menace to scientific workers. The lung of the same baby had in it also several minute encapsulated areas of caseation. Gram-positive cocci, molds and organisms looking like ray-fungi were found in and near the areas. They may provisionally be considered as encapsulated abscesses, probably following broncho-

125 Shattock, S. G. *Lancet* 1:319, 1909.

pneumonia Wilson<sup>122</sup> also found silicosis in the lung of a Basket-Maker body, associated with a pleural adhesion. In Egyptian mummies Smith and Dawson<sup>6</sup> and Wood-Jones<sup>13</sup> observed pleural adhesions. Ruffei<sup>1</sup> referred to anthracosis, and particularly to two cases of pneumonia. One of these was observed in a mummy of the Greek period, the lungs of which contained many bacilli that reminded him strongly of plague bacilli.

Apparently not many specimens of the stomach and intestines have been examined. The character of the food may be, in part, determined from their contents. Considering the alleged traditional prevalence of *Taenia saginata* in Abyssinia, one might expect to find tapeworm eggs in the intestines of ancient Nubians and Egyptians, if they ate beef. In general, the eggs of parasitic worms would stand a good chance of being preserved. Wood-Jones<sup>1</sup> mentioned prolapse of the intestine and vagina, also an old appendicitis.

Ruffei<sup>120</sup> described what seems to have been cirrhosis of the liver.

Smith and Dawson<sup>6</sup> referred to a single case of gallstones, the only one thus far found in Egyptian mummies.

Smith and Dawson<sup>6</sup> said that two cases of vesical calculus and three of stone in the kidney had been discovered in an examination of about 30,000 ancient Egyptian and Nubian bodies. One of these was found in a predynastic body. Wood-Jones<sup>13</sup> and Ruffei<sup>120</sup> also referred to vesical calculi, whether or not these two instances are included in the preceding statement is not clear. Ruffei observed a case of multiple abscesses of the kidney with many gram-negative bacilli. Williams<sup>126</sup> described a vesical calculus of mixed composition (fig. 15) from the body of a male Basket-Maker about 18 years old excavated in Arizona.

Vesicovaginal fistula is shown in the mummy of Princess Hehenit, eleventh dynasty. According to Derry,<sup>127</sup> "The injury is associated with an abnormally narrow pelvis, and it seems fair to suggest that it was probably produced during a difficult labor, and caused the death of the mother, who was quite young." Derry<sup>128</sup> also described a case of death of a Negress in childbirth discovered in remains from a Coptic cemetery. The fetal head was firmly wedged in the narrowed pelvis. The right sacro-iliac joint was missing (probably congenitally) and the right innominate bone was small, producing the distortion of the pelvis. The left sacro-iliac joint gaped widely, and there was overriding of the cranial bones of the fetus.

126 Williams, G. D. An Ancient Bladder Stone, J. A. M. A. **87** 941 (Sept 18) 1926.

127 An account of this case, which will probably have been reported by Naquib Mahfouz before the present paper has been published, was given to me by Prof. Douglas E. Derry, of the Anatomy Department, Egyptian University, Cairo (personal communication).

128 Derry (footnote 77, p. 48).

The evidence of dystrophia adiposogenitalis or Froelich's syndrome in the case of King Akhenaton was related in the introduction

Several of the royal mummies of Egypt showed appearances of the skin that may be all that is left of the eruption of some disease, but it was not possible to be certain, these evidences were mentioned by Smith<sup>6</sup> and Ruffer.<sup>120</sup> Baldness was frequent and comedones not rare. Several ulcers of the skin were found. Wilde<sup>119</sup> reported minute whitish granules on the skin of a Peruvian mummy, which appeared to be bacterial foci, and which might be the relics of some disease of the skin.

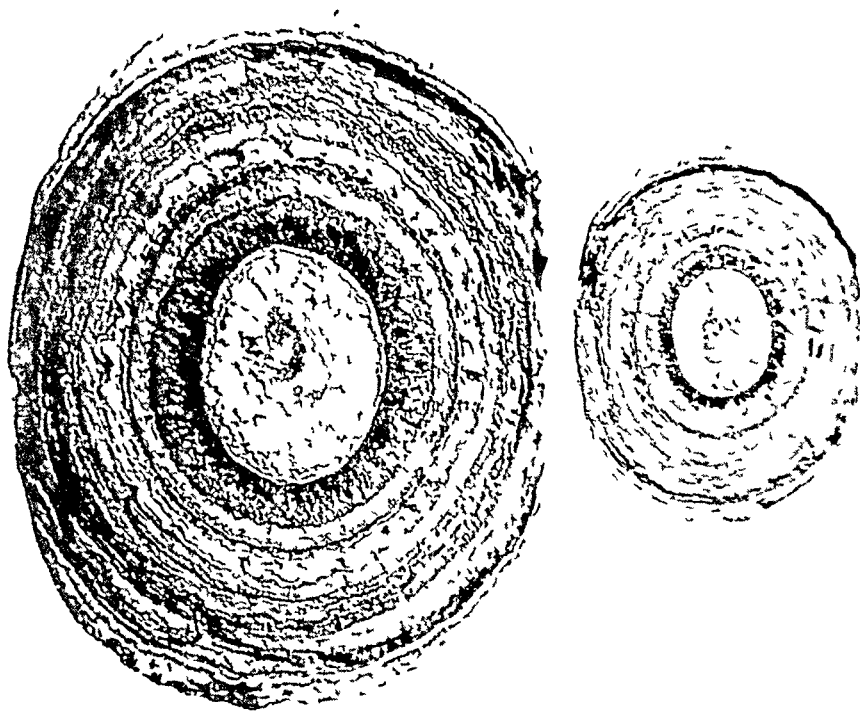


Fig. 15—Calculus (natural size and magnified) from the urinary bladder of a Basket-Maker body. The photograph was sent me by Dr. George D. Williams, Washington University, St. Louis.

The occurrence of gout was observed by Wood-Jones<sup>13</sup> in an early Christian body from Egypt, which is described in considerable detail by Smith and Dawson.<sup>6</sup>

A single case of leprosy had been found up to 1924. This was in a body of early Christian date. It is mentioned by Smith and Deery<sup>75</sup> and by Smith and Dawson,<sup>6</sup> who give illustrations. Although leprosy bacilli were sought for, none were found. Innumerable cocci were present in the sections.

Rolleston<sup>129</sup> described the skeleton of a neolithic flint miner from Cissbury, England, with shortening of the bones of the left arm, which he attributed to poliomyelitis. The left humerus was  $1\frac{3}{10}$  inches (3.25 cm) and the left radius  $\frac{8}{10}$  inch (2 cm) shorter than the right. An Egyptian skeleton in the Archeological Museum of the University of Pennsylvania has shortening of the left femur to the extent of 8.2 cm, while the circumference of the shaft is somewhat reduced. This specimen was described by Mitchell,<sup>130</sup> who made a provisional diagnosis of poliomyelitis. The skeleton, excavated by Flinders Petrie, was said to belong to a period about 3700 B.C. The skeleton was that of an old man, and a slim staff buried with it was thought to have been used by him for balancing. It will be noted that the ancient man whose skeleton is next to be described also carried a staff.

The ancient Egyptian stela shown in figure 16 (described by Hamburger<sup>131</sup> and by Slomann<sup>132</sup>) may have been intended to represent the atrophy of one leg from poliomyelitis, though other causes of such atrophy must be entertained. Slomann contended also that the talipes equinus shown by the mummy of the Pharaoh Siptah, described and illustrated by Smith,<sup>27</sup> was due to poliomyelitis, probably occurring in childhood.

At the instance of Smith, a mummy of the twentieth dynasty (from 1250 to 1000 B.C.) showing an eruption resembling smallpox was studied by Ruffer and Ferguson,<sup>133</sup> who removed a portion of the skin for sectioning. Their modest assertion that the eruption resembles smallpox is justified by the illustrations of the gross appearance and of the sections as seen under the microscope. Numerous gram-positive bacilli and a few micrococci were demonstrated in the tissue. It was not supposed that these organisms played any part in the disease, but it was thought that they were present at or near the time of death. This case was criticised by Unna, to whom Ruffer<sup>134</sup> subsequently replied. In this second article, Ruffer seems to refer to the mummy in question as of the eighteenth dynasty. He mentioned a similar eruption on the mummy of Rameses Fifth, who belonged to the twentieth dynasty. Smith and Dawson<sup>6</sup> mentioned an eruption resembling smallpox on the body of Rameses Fifth. Ruffer's statements are not clear to me, but I should conclude that two such cases have been found in Egyptian mummies.

129 Rolleston, G. H. *J. Anthropol. Inst. Great Britain & Ireland* **7**, 377, 1878.

130 Mitchell, J. K. *Tr. A. Am. Phys.* **15**, 134, 1900.

131 Hamburger, O. *Bull. Soc. franç. d'hist. de la med.* **10**, 407, 1911.

132 Slomann, H. C. *Contributions à la paleopathologie Égyptienne*, *Bull. et mem. Soc. d'anthrop.*, Paris **8**, 62, 1927.

133 Ruffer, M. A., and Ferguson. *J. Path. & Bact.* **15**, 1, 1911. Ruffer (footnote 1, second reference, p. 32).

134 Ruffer (footnote 120, fifth reference, footnote 1, second reference, p. 175).

A few enlarged spleens found by Ruffer may have been from ancient patients with malaria, the evidence for malaria is not powerful

Tuberculosis has been discussed in connection with diseases of the bones



Fig 16—A stela in polychrome from Egypt, of the period of the eighteenth dynasty (from 1580 to 1350 B C ) The dimensions are 27 by 18 cm It is thought to represent the results of acute poliomyelitis The photograph was sent me by Dr H C Slomann, of Copenhagen The stela is in the Glyptothek of Ny Carlsberg in that city

Wilde<sup>119</sup> spoke of a small species of mite (Acarina) that he observed in the stomach contents, uterus and nasal cavity of a Basket-Maker body associated with masses of what appeared to be blood corpuscles, suggesting a parasitic habit



One of the most brilliant discoveries thus far made in paleohistology was achieved by Ruffer<sup>135</sup> when he found the eggs of *Schistosoma* (*Bilharzia*) in the kidneys of two mummies of the twentieth dynasty (from 1250 to 1000 B C). As the disease produced by *Schistosoma* is exceedingly common in Egypt at the present day, the demonstration of its occurrence at such a remote period in the same locality becomes one of extraordinary interest. Eggs of lice were also found by Ruffer adhering to the hair of mummies.

#### PATHOLOGIC OBSERVATIONS IN ANCIENT ART

Art as depicting pathologic conditions of early times is considered at length in such works as that of Paul Richer. In the present article, it will be possible only to allude to a few of the more ancient examples.

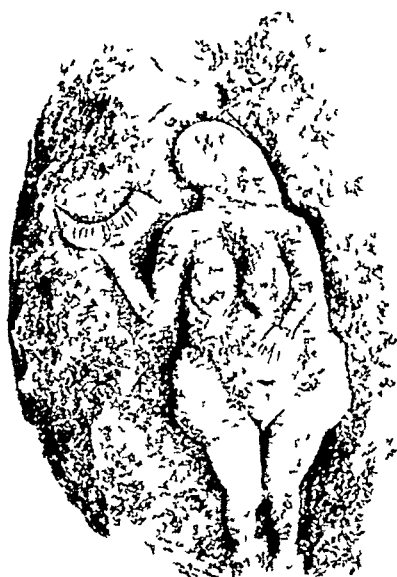


Fig 17—Carving of a human figure excavated by Dr G Lalanne, of Bordeaux, at Laussel (Dordogne) in southwestern France, in 1911. It was carved in high relief on a block of limestone, about 67 cm long. It belongs to the upper Aurignacian division of the late paleolithic period, and is probably around 25,000 years old. Figures of this kind are the oldest known portraits of man. A number of such have been found, frequently in the form of statuettes, over the region extending from southwestern France to Czechoslovakia. Such figures of steatopygous females are usually called venuses, and this one is the "Venus of Laussel."

In view of the fact that painters of the renaissance, as, for example, Velasquez, were fond of picturing persons with chondiodystrophy, cretinism and the like, similar efforts on the part of more primitive artists do not occasion surprise. The carvings, engravings and paintings of the cave artists of the reindeer period (from about 15,000 to 30,000

<sup>135</sup> Ruffer (footnote 1, second reference, p 18), Brit M J, Jan 1, 1910, p 16

years ago), found especially in southern France and northern Spain, excite one's wonder and admiration by their accurate drawing and their lively spirit. MacCurdy,<sup>8</sup> who always succeeds in interpreting the work of primitive races with deep sympathy, remarked that men were artists before they became farmers. Unfortunately for our purposes, the cave artists chose for their models, for the most part, large mammals, like the reindeer, bear, mammoth and rhinoceros, they rarely drew their own kind. Several human figures in the form of steatopygous females have, however, been found (fig 17). While not pathologic, the prominence of the secondary sexual characters is notable. Such figures, ironically called venuses, may have been symbolic, but they must also have been fashioned after models and may be considered as portraits, they are, besides, of unusual interest because, even if not flattering to our species, they are the earliest portraits of the human being known. The resemblance to the Hottentot female has often been remarked.<sup>136</sup>

The curious practice of mutilating the hands by amputation of one or more fingers has been employed by many primitive peoples as part of some ritual or sacrifice. Plain evidence that this custom prevailed among the cave artists is given on the walls of the caves where the hand was applied to the rock while some red coloring material was painted around it as with a stencil.<sup>137</sup>

Ancient Egyptian art reproduced figures of several pathologic conditions, which were described in an interesting article by Ruffer.<sup>28</sup> He gave illustrations of achondroplastic dwarfs 5,000 years old, of persons with talipes equinovarus 4,000 years old and of other figures that he believed represent persons with Pott's disease and rickets, which are about 4,000 years old. The same subject was later reviewed by Dawson,<sup>28</sup> who also gave numerous illustrations.

Slomann<sup>132</sup> discussed several figures from Egyptian art, which he believed represent, respectively, Pott's disease of the spine, a humpback that may be rachitic, achondroplastic dwarfism, congenital dislocation of the hip and (fig 16) what may well be the atrophy of one leg from poliomyelitis (eighteenth dynasty, from 1580 to 1350 B C). A good example of a pathologic condition shown in ancient Greek art is a statuette representing an ulcerating tumor of the breast.<sup>138</sup>

In America, the specimens of native art that attempt to delineate disease are largely confined to representations of the human body in pottery. The earliest note on such figures that I have met is in an

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136 Zelisko. Einige Bemerkungen zur Frage der Steatopygie des Paleolithischen Menschen, abstr, *Am J Phys Anthropol* 7 463, 1924.

137 This subject is thoroughly treated and examples from America shown by Smith, V J. *Pub Texas Folk-Lore Soc*, 1925, no 4.

138 Long, E R. *History of Pathology*, Baltimore, Williams & Wilkins Company, 1928.

article by Whitney<sup>14</sup> referring to images apparently meant to depict hunchbacks, from the "stone graves" of Tennessee<sup>139</sup>

Spinden,<sup>140</sup> a believer in the American origin of yellow fever, gave drawings of certain pictures of the Aztecs, which he thought were meant to represent the "blood vomit" of yellow fever, they are not entirely convincing

The pottery of Peru, as seen in the museums, shows many models of the human figure. Curious and unusual sexual practices that may be of interest to psychiatrists are sometimes vividly depicted. Much



Fig. 18—Two clay figures (huacos) in the Peabody Museum, Cambridge, Mass., representing some form of ulcerative disease. They came from a prehistoric cemetery at Chimbote, Peru. The photographs were made for this article by Samuel J. Guernsey.

discussion has been occasioned by specimens of pottery (called huacos) that appear to show the results of ulcerative lesions of the face, especially about the nose, and others representing nodules of the face and, less often, of other parts of the body (fig. 18). Leprosy, lupus, syphilis, verruca peruana, yaws, gundu and uta all have been suggested as dis-

<sup>139</sup> Moodie (footnote 18, p. 472, plate XCI) gave a photograph of such an image.

<sup>140</sup> Spinden, H. J. Yellow Fever, *World's Work* **43**, 169, 1921.

eases that the Peruvian artists intended to represent. Some specimens may have been intended to depict dwarfs, congenital malformations, intentional mutilations or the results of surgical operations, such as amputations. Recent opinion is disposed to regard many of the lesions shown on these images as attempts to represent *uta*, an ulcerative disease, usually of the face, especially of the region about the nose, which is still common in Peru. Strong<sup>141</sup> and his colleagues regarded *uta* as a form of leishmaniasis. A considerable literature has grown up in the discussions over these clay images from Peru.<sup>142</sup>

#### SUMMARY

The preceding review of what has been accomplished in studies on human paleopathology has led to certain conclusions, the most important of which I shall present in this brief summary.

Rickets seems to have been rare in ancient times. Rickets leaves changes in the bones so definite that, if present, they could hardly be overlooked. One encounters, however, a curious and striking condition, usually called symmetrical osteoporosis of the skull, which may be allied to rickets or scurvy or to some of the anemias of children, and which seems to occur rarely, if at all, among modern white peoples. Symmetrical osteoporosis was frequent among American Indians in the area where the cultivation of Indian corn or maize was most highly developed.

Arthritis deformans afflicted ancient peoples of both continents at least as often as it does today. The number of studies that consider a possible relation between arthritis deformans and diseases of or about the teeth in ancient times is so small as to be negligible. Such studies are much to be desired, but are made difficult by the fact that skulls are so often separated from the rest of the skeleton and many of the teeth in them lost post mortem. Several observers attributed arthritis deformans among the ancients to cold and moisture, but these observations were made, for the most part, about twenty years ago.

Arteriosclerosis prevailed in ancient Egypt in the same manner as it does among modern people, so far as the nature of the material permits us to form conclusions, a single case was found in a body from ancient Peru, among probably fewer than half a dozen bodies examined.

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141 Strong, R. P., et al. Report of First Expedition to South America, Harvard School of Tropical Medicine, Cambridge, Harvard University Press, 1915, p. 175.

142 The earlier literature is largely given in the article of Lehmann-Nitsche, Robert. *Patologia en la Alfareria Peruana*, Rev. Museo de la Plata **11** 29, 1902. More recent literature is given in the report of Strong (footnote 141) and Moodie (footnote 18, p. 488). One of the first in this field was Ashmead, A. S. J. *Cutan & Ven. Dis.* **13** 465, 1895, *ibid.* **14** 53, 1896, *Am. Anthropol. N. S.* **9** 738, 1907. Other papers by Ashmead are cited in Lehmann-Nitsche.

Anthraxosis and silicosis are often found in ancient bodies. A few or single cases of the following diseases have also been demonstrated: pleural adhesions, pneumonia, cirrhosis of the liver, appendicitis, biliary and urinary calculi and gout.

Tumors of bone, in the form of small osteomas, were not rare. Osteosarcoma (or osteogenic sarcoma) must have been rare in ancient times. Even the great collections of bones from Egypt and from Peru and other parts of America have yielded only a small number of examples. This tumor often produces new growths of bone so startling that no collector could overlook them. Although osteosarcoma is perhaps not a common tumor today, every large museum of pathology has several modern specimens. It would be rash to say that this tumor has become more frequent in modern times, but it is proper to state the facts.

Carcinoma may erode the bones, especially of the face, the destruction so wrought could not fail to attract attention. I have been able to learn of only an insignificant number of ancient cases of this kind. However, erosion by cancer would often be difficult to distinguish from the postmortem erosion of bone by natural causes.

The teeth of ancient peoples were usually ground down or worn down by coarse food or dirt more than are the teeth of modern or civilized races. Dental abscesses and the condition known as pyorrhea alveolaris and as periodontoclasia and by a multitude of other names seem to have been at least as common in ancient times as they are at present, pyorrhea has been reported even as occurring in Neanderthal man. Dental caries was stated by some investigators to have made its appearance first in the neolithic period. However, it should be remembered that the amount of material for study from the earliest periods is not to be compared with what is available from later periods, it is by no means certain that the last word has been said as to the date when men first began to have decay of teeth. In general, students seem to agree that dental caries was less common in the ancient periods than it has become in modern times, also that it became gradually more frequent as living conditions approached or merged into those of modern civilization. But what factor (or factors) in modern life is the one productive of dental caries has thus far defied analysis. The results to date certainly indicate that extensive studies on diet in relation to dental caries are needed.

Tuberculosis has been identified, in all reasonable probability, in Egyptian mummies that can be assigned to 2700 to 1100 B.C. The evidence in the scanty material from neolithic Europe is less convincing and that in the skeletal remains of ancient Americans must be called indecisive, leaning toward the negative.

Leprosy has been traced in pathologic material to but one probable case belonging to early Christian times in Egypt

Poliomyelitis was probably present in neolithic Europe, and in Egypt as early as 3400 B C , the evidence is suggestive, but not conclusive

Smallpox was the probable cause of certain lesions found in Egyptian mummies of 1250 to 1000 B C

Schistosomiasis was demonstrated in Egyptian bodies of 1250 to 1000 B C

Human paleopathology presents attractive possibilities for work in the future. Some of the large museums have great collections of ancient bones that have been examined only partially or not at all for conditions of disease. The teeth are particularly promising. Cooperation between archaeologists, physical anthropologists and pathologists should bring about results useful to all three. The pathologists have already been useful to the archaeologists and the historians in problems relating to the identification of bodies. While the possibilities in the examination of dried and mummified bodies are limited they are fascinating. If the soft parts, as well as the bones, of all available mummies, could be studied by competent pathologists, as the bodies of patients dying in modern hospitals are studied, much information, I am confident, would be gained on disease in ancient times.

## Notes and News

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**University News, Promotions, Resignations and Appointments**—Wiley Davis Forbus, associate in pathology in Johns Hopkins University, has been appointed professor of pathology in Duke University, Durham, N C

Novoa Santos of the University of Galicia has been made professor of general pathology in Central University, Madrid, Spain

The William Wood Gerhard medal of the Philadelphia Pathological Society has been awarded to F d'Herelle, now professor of bacteriology in Yale University, for his work on bacteriophage

Werner Gunlach, Hamburg, Germany, has been called to the professorship of pathology in the University of Halle

John R Cuff has been appointed research fellow, and John A Ferguson instructor in pathology, in the Harvard Medical School

Maurice L Cohan has been appointed instructor in pathology and bacteriology in the University of Illinois College of Medicine

Kenneth Fowler has been appointed director of laboratories in the Jewish Hospital, St Louis

Charles H Best has been appointed professor of physiology in the University of Toronto to succeed J J R McLeod who becomes professor of physiology in the University of Aberdeen

Eugene L Opie, director of the department of pathology in the University of Pennsylvania and of the laboratory of the Henry Phipps Institute, has been elected a member of the board of scientific directors of the Rockefeller Institute for Medical Research

Katsusaburo Yamagiwa of the University of Tokyo has been awarded the Sophie A Nordhoff-Jung Cancer Prize of \$1,000 for his work on producing cancer in animals by means of tar This is the third award of this prize, the previous recipients being the late Johannes Fibiger and Otto Warburg

Ernest M Hall has been appointed professor of pathology and bacteriology in the school of medicine of the University of Southern California, Los Angeles

Leonor Michaelis of the Johns Hopkins University School of Medicine, has been appointed to the staff, with the title of member, of the Rockefeller Institute for Medical Research, New York

**Frederick W Andrewes Honored**—Number 2, volume 32, of the *Journal of Pathology and Bacteriology* (April, 1929) is dedicated to Frederick William Andrewes on his seventieth birthday, March 31, 1929

**American Association of Pathologists and Bacteriologists**—The next meeting of this association will be held in New York, April 17 and 18, 1930

**Formation of Pathologic Society in San Francisco**—On April 22, 1929, an organization to be known as the San Francisco Pathologic Society was formed A constitution and by-laws were adopted and the following officers were elected president, William Ophuls, vice president, G Y Rusk, secretary-treasurer, Z E Bolin, executive committee, C L Connor, A M Moody and W T Cummins It is interesting to note that a similar society was formed in 1851 in San Francisco and that this was one of the earliest medical organizations on the Pacific coast

**Death of Alexander Ogston**—Alexander Ogston, regius professor of surgery in the University of Aberdeen and a pioneer student of the bacteriology of inflammation and suppuration, to whom is owed the discovery of staphylococci, died on Feb 1, 1929, at the age of 84 years He introduced the name *Staphylococcus* His name will have "a permanent place in the history of pathogenic bacteriology in its classical period"

**Pathologic Society of Great Britain and Ireland**—The next meeting of this society will be held at Cambridge on July 5 and 6, 1929

# Abstracts from Current Literature

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## Experimental Pathology and Pathologic Physiology

EXPERIMENTAL PURPURA WITH ANTI-PLATELET SERA ROSCOE R. HYDE, *Am J Hyg* 8 870, 1928

Miliary purpura was produced on the skin of a guinea-pig by the intravenous administration of antiplatelet serum, the attack being initiated by shaving the skin over the abdomen. A deficiency in complement did not prevent the appearance of the purpura. Subjection of the antiplatelet serum to repeated absorptions with excessive amounts of boiled corpuscles without effect would indicate that the antibody is evidently not of the nature of a heterophile immune body. Purpura produced by antiplatelet serum is intensified in animals whose blood has been previously rendered incoagulable by the anti-coagulant heparin.

PEARL ZEEK

THE EQUATION EXPRESSING THE EXCRETION OF A DIURETIC AND ITS RELATION TO DIFFUSION PROCESSES E. J. CONWAY, *Am J Physiol* 88 1, 1929

Proceeding from the theory that the total volume of urine comes from the glomeruli, being similar in composition to a blood filtrate, and that all substances appearing in the urine in greater concentration than in the blood are added by diffusion from the tubule cells, the author develops theoretical formulas to cover various relations between the plasma and urine. Of the several formulas presented, perhaps the one of most direct application is

$$\sqrt{\frac{1}{t} \frac{C_u}{C_b}} = \text{constant}$$

which shows the diffusion-secretion relations of urea excretion in the human being, this has been shown by statistical analysis to be the true relation for volumes of urine up to approximately 4 liters per day. Evidence is presented to show that sulphates and phosphates follow the same relationship. As to the constancy of the relationship of the output of urea to the blood concentration at high volumes of urine and normal blood concentrations, the author presents reasons to indicate that this may be due to the fact that available renal energy reaches a limit with high volumes of urine, approximately 4 liters a day.

H. C. EGGERS

THE EQUATION EXPRESSING THE EXCRETION OF A DIURETIC AND ITS RELATION TO DIFFUSION PROCESSES E. J. CONWAY and F. KANE, *Am J Physiol* 88 29, 1929

The threshold value of chloride was found by the authors to be 0.574 per cent for the rabbit, a figure practically identical with that obtained for the human being by McLean. ("Threshold value" is regarded as the highest limit of plasma concentration at which the urinary concentration is less than plasma concentration for all rates of flow of urine.) This value was not affected by injections of dextrose even in large amounts, but was increased by the injection of sulphate or of urea. The theory of the chloride excretion, advocated by the authors, is that its concentration in the urine is determined, after primary discharge, by the rate and direction of chloride diffusion during the passage of the urine along the tubular tracts, the water output being regulated solely at the glomerulus. From premises based on this theory, they show that the rate of absorption of sodium chloride is directly proportional to  $(T - C_b)$ , when  $T$  is threshold value and  $C_b$  is blood concentration, and that with a constant value of blood concentration, the rate of absorption is proportional to  $t$ ,  $t$  being the time of a unit volume of urine. These relationships are closely analogous to the diffusion of iodine from chloroform into aqueous solutions of potassium iodide, and are in harmony with facts established in other lines of renal investigation.

H. E. EGGERS



EFFECT OF CORPUS LUTEUM AND OVARIAN EXTRACTS ON THE OESTRUS OF THE GUINEA-PIG D I MACHT, A E STICKELS and D L STECKINGER, *Am J Physiol* **88** 65, 1929

A study was made of the effects of specially prepared water extracts of corpus luteum on the estrus cycle of the guinea-pig by means of the vaginal smear method. The extracts were found to produce inhibition of estrus, and this inhibition was accompanied by characteristic histologic observations in the ovaries, consisting of a diminution of maturing follicles and a tendency toward the development of atretic follicles. The injection of other glandular extracts was without this effect, only placental extracts tended toward a similar action. It was observed that in the presence of even slight pyogenic infection, the estrus was affected to the point where the sexual cycle became decidedly irregular.

H E EGGERS

THE EFFECT OF DAILY TRANSPLANTS OF THE ANTERIOR LOBE FROM GONADECTOMIZED RATS ON IMMATURE TEST ANIMALS E T ENGLE, *Am J Physiol* **88** 101, 1929

On transplanting daily the fresh anterior lobe of the pituitary from gonadectomized rats into immature females, the ovarian response was definitely greater than when the similar tissue from normal rats was transplanted. There was no sex difference in respect to the gonadectomized animals, and no significant differences as regards the age of the donor at the time of gonadectomy. The ovarian response was so much greater that in addition to the increased size of the pituitary in the gonadectomized animal, it is believed that there was an additional storage of the gonadal stimulating factor. These results are explained by the author as indicating the existence of a gonadal-pituitary "releasing mechanism," the presence of the gonad being of prime importance in releasing the hormone from its site of origin.

H E EGGERS

THE EFFECT OF MASSAGING THE THYROID ON THE BASAL METABOLIC RATE OF DOGS O B DE COUTO-E-SILVA and C S SMITH, *Am J Physiol* **88** 183, 1929

In trained dogs, without anesthesia and under conditions as nearly physiologic as possible, external massage of the thyroid gland for half an hour was found to produce no immediate and little, if any, delayed increase in the metabolic rate.

H E EGGERS

EXPERIMENTAL STUDIES ON DENERVATED LUNGS R FONTAINE and L G HERRMANN, *Arch Surg* **16** 1153, 1928

In the dog, partial denervation of one lung is a safe procedure, and can be accomplished by unilateral resection of the first four thoracic sympathetic ganglions and removal of the ansa vieussenii and the stellate ganglion, together with the resection of the portion of the vago-sympathetic trunk which has included in it the middle cervical ganglion. The authors find that section of these nerves that lead to one lung does not cause any change in the frequency or character of the respiratory movements. Such a lung shows no difference in reaction to stimuli from the intact one. The carbon dioxide combining power of the plasma is not affected. The occurrence of massive collapse is not prevented.

N ENZER

PROBABLE EFFECT OF PANCREATIC JUICE ON THE REGULATION OF GASTRIC ACID R ELMAN, *Arch Surg* **16** 1256, 1928

During drainage of the total pancreatic juice the gastric contents contain far higher total and combined acid than normal. Acid solutions introduced into the stomach of animals during such drainage provoke an intense increase in the flow

of pancreatic juice to the outside Drainage of pancreatic juice is accompanied by regurgitation of the intestinal contents into the stomach The injected acid is not neutralized as in the normal animal The author states that this evidence supports the hypothesis that the reduction of gastric acid results from the reflux of alkaline pancreatic juice into the stomach

N ENZER

INFLUENCE OF LIGHT ENVIRONMENT ON NORMAL RABBITS WADE H BROWN,  
J Exper Med 49 103, 1929

A series of experiments was carried out for the purpose of determining whether a light environment comprising radiations of comparatively long wave length and of only a small amount of energy was capable of affecting the chemical equilibrium of the blood as indicated by the calcium and inorganic phosphorus content of the blood of normal rabbits A study was made of effects produced by prolonged exposure to fixed environmental conditions (neon light and darkness) as compared with a varying environment of diffuse, filtered sunlight, and by a change from one environment to another It was found that the chemical equilibrium of the blood was definitely affected by the conditions employed and that the effects produced could be correlated with differences in organic constitution on the one hand, and on the other, with certain differences in the functional activity of the same animals, involving nutrition, growth and the proliferative activity of hair follicles

AUTHOR'S SUMMARY

CALCIUM AND PHOSPHORUS METABOLISM WALTER BAUER, JOSEPH C AUB  
and FULLER ALBRIGHT, J Exper Med 49 145, 1929

The trabeculae of the bone are easily depleted by the prolonged administration of parathyroid extract-Collip, long continued negative calcium balance and growth A long continued high calcium diet results in a rapid accumulation of the trabeculae Alizarin red, as has previously been shown in the literature, is deposited in newly formed bone Its use has made clear that easily mobilizable calcium is not deposited in the shafts of adult animals, but in the trabeculae of bone The bone trabeculae therefore serve as the storehouse of readily available calcium The shafts have a slow, progressive exchange of inorganic salts and are not influenced except in the case of unusual demands of the body It is suggested that the absence of trabeculae in premature infants and their depletion at the end of four months in a normal baby might well be an etiologic factor in rickets In these observations, the administration of parathyroid extract-Collip to growing or adult cats has been without effect Daily injections of parathyroid extract-Collip in growing rats result in an increased number of trabeculae and smaller bones

AUTHORS' SUMMARY

THE CHEMICAL NATURE OF THE SUBSTANCES REQUIRED FOR CELL MULTIPLICATION LILLIAN E BAKER, J Exper Med 49 163, 1929

It has been shown that the ash of liver, hemoglobin and glutathione each exerts a slight beneficial effect on the growth of sarcomatous fibroblasts of the rat, or on the condition of their cells when cultivated in a synthetic medium The addition of all three of these substances, or of only glutathione and hemoglobin, to a mixture of casein digest, glyocoll and nucleic acid gives a medium in which sarcomatous fibroblasts of the rat proliferate for a considerable time as rapidly as in embryo juice The mixture is not as adequate a nutritive medium as embryo juice, for after a time dead cells are found surrounding the central fragment of the culture, and after several passages the growth becomes thinner The hypothesis is suggested that glutathione and hemoglobin may function not only by regulating the respiration and oxidation reduction reactions within the cell, but also by regulating the oxidation-reduction potential of the medium It is suggested that the failure to obtain growth of fibroblasts in mixtures of amino-acids or of

the products of complete acid hydrolysis of proteins is in part due to the absence of glutathione, and that this substance is not synthesized by fibroblasts. The growth of normal fibroblasts of the rat is also increased by the addition of the aforementioned substances to a synthetic medium

AUTHOR'S SUMMARY

BLOOD REGENERATION IN SEVERE ANEMIA F S ROBSCHUIT-ROBBINS and G H WHIPPLE, *J Exper Med* **49** 215, 1929

A liver extract, no 343, N N R, known to be fully potent in pernicious anemia shows only from 10 to 20 per cent of the potency of whole liver when fed to dogs for severe continuous secondary anemia due to bleeding. There are wide individual variations which are not noted when whole liver is fed. Supplementing this liver extract with whole bile does not modify the reaction. Supplementing the liver extract with liver ash or apricot ash shows the sum of the two expected feeding reactions. When this liver extract is supplemented with small amounts of whole liver (from 50 to 100 Gm) there is a production of hemoglobin and red cells in excess of the sum of the expected separate reactions. Whether the liver extract increases the potency of the whole liver or vice versa, it suggests similar possibilities in various human secondary anemias. Liver and kidney fractions of varied types deserve much study to ascertain their effect on widely divergent types of anemias in human beings

AUTHORS' SUMMARY

THE RELATION OF FREQUENCY TO THE PHYSIOLOGICAL EFFECTS OF ULTRA-HIGH FREQUENCY CURRENTS RONALD V CHRISTIE and ALFRED L LOOMIS, *J Exper Med* **49** 303, 1929

The biologic effects of electromagnetic waves emitted by a vacuum tube oscillator have been studied at frequencies ranging from 8,300,000 to 158,000,000 cycles per second (a wave length of from 1.9 to 38 meters). The effects produced on animals can be fully explained on the basis of the heat generated by high frequency currents which are induced in them. No evidence was obtained to support the theory that certain wave lengths have a specific action on living cells. At frequencies below 50,000,000 cycles, the effect of these radiations on animals is proportionate to the intensity of the electromagnetic field. As the frequency is increased beyond this point, the amount of induced current is diminished and the apparent lethality of the radiation is decreased. This can be explained by changes occurring in the dielectric properties of tissues at low wave lengths

AUTHORS' SUMMARY

INTERMEDIATE METABOLISM OF FAT IN HEPATIC DISEASES C CASSANO, *Arch di pat e clin med* **7** 441, 1928

In all the cases of hepatic diseases studied, it was established that the fat metabolism is greatly disturbed, and that the resulting lipemic conditions are usually due to a retardation of the intermediate fat metabolism. The increase of the neutral fats and the decrease of the phosphatids is a constant result. There are no special types of hepatic disturbances of fat metabolism that would correspond to a definite diseased condition of the liver, the disturbances reveal only the degree but not the character of the hepatic lesion. The functional insufficiency of the liver in metabolism of fats commonly varies in intensity and often exhibits new pictures of metabolic disturbance. The fatty acids appear increased, indicating the inability of the liver to split them. They are partly bound with cholesterol, forming cholesterol esters. As a rule, there is an increase in cholesterol which appears necessary in order to assure the synthesis and the diuresis of the phosphatides. It seems that the cholesterol, which are regulated by the liver, neutralize the toxic action of the fatty acids. The anatomic and functional lesions of the liver are accompanied by varied disturbances in the chemical behavior of the cholesterol, phosphatides and fatty acids

E L MILOSLAVICH

# FACTORS ASSISTING THE HEART IN ITS WORK AS A SUCTION AND PRESSURE PUMP G HAUFFE, Virchows Arch f path Anat **266** 18, 1927

The circulation of the blood is maintained by the heart alone, through the opposing movements of the walls in the auricles and ventricles. This opposing movement is achieved by the enclosure of the heart in the pericardium. The system of the pericardium and heart acts as a suction and pressure pump while the conduction system maintains proper correlation between the two forces. In the circulating blood, the movement is influenced by various secondary factors, activated by the central motor, the elasticity of the vessel walls, valves in the veins, etc. These maintain the original speed as nearly as possible to the end, and disappear when the work is accomplished. Systolic stretching of the aorta does not occur, and the capillaries do not act as a resistance to the blood stream. Distribution of the blood in the service of respiration of the cells is effected by certain organic forces. These forces perform the work of changing the width of the blood vessels, and therewith are dissipated. They, as well as the other factors assisting the circulation, must be set in motion afresh each time by the heart through its suction activity.

B R LOVLTT

# DIFFERENCES IN RESISTANCE OF THE FEMALE AND MALE SEX GLANDS H V KLEIN, Virchows Arch f path Anat **266** 18, 1927

The longer persistence of sexual activity in the testis than in the ovary may be explained by differences in the resistance of the two glands or on the basis of inherited, sex-limited characteristics. From the literature, it appears that the ovary is in general more resistant than the testis to operative procedures, partial removal, thermal and chemical injuries. The regenerative power of the ovary is greater, and in autotransplants it lasts longer.

The author's experiments with autotransplants in rabbits and guinea-pigs showed, in the case of males, marked individual differences in the results. In some, the sexual function of the transplants persisted, while in others it was completely lost. In one female there was persistence of function, although the transplanted organ disappeared completely. Roentgen irradiation of the ovaries was followed by sexual hyperactivity, probably due to premature rupture of follicles with the escape of sex hormone into the blood. No analogous result occurred in males. Klein concluded that the ovary is more resistant than the testis. Its cessation of function after the fifth decade cannot be explained entirely on the teleologic basis, that woman is not fitted to go through pregnancy after this time, but belongs to the picture of the genotype of the human female.

B R LOVLTT

## Pathologic Anatomy

### INTUSSUSCEPTION DUE TO PAPILLOMA IN A CHILD OF TWENTY-ONE MONTHS EDWARD J LAMB, Am J Dis Child **36** 1017, 1928

Papillomas of the small intestine are rare and intussusception caused by papilloma is of rare occurrence. When polypoid growths occur in the intestine they are apt to be multiple. Recovery of an infant after resection for invagination ileus is a surgical curiosity.

AUTHOR'S SUMMARY

### A CASE OF PYOSALPINX CAUSED BY OXYURIS VERMICULARIS COMPLICATED BY TORSION OF THE OVIDUCT W SMITH and J DENTON Am J Obst & Gynec **16** 205, 1928

This interesting case occurred in a nullipara, 23 years of age, who for six weeks had pain in the lower right part of the abdomen which grew progressively worse. The blood count and eosinophil ratio were practically normal. At laparotomy the right tube was found twisted from left to right, distended and cystic, the left tube

was likewise enlarged. The wall of the left tube was enlarged due particularly to a thickening of the mucosa and submucosa, and here an extensive infiltration of round cells could be seen. There were numerous foreign body giant cells close to sections of the worm. The similarity of this process to tuberculous reaction of the fallopian tube was observed.

A J KOBAK

ECTOPIC CORPORA LUTEA. VERA B. DOLGOPOL, *Am J Obst & Gynec* **16** 218, 1928

The term "ectopic corpora lutea" is proposed by Dolgopol for corpora lutea that becomes partially or totally separated from the ovary. The author added six cases to the twenty-four previously described in the literature and pointed out an omission of this condition in the English literature. Since the cases described by the author all occurred in five months, with a similar frequency cited in another report, it was suggested that this condition may be overlooked by surgeons. No untoward symptoms were associated with this condition.

A J KOBAK

ENDOMETRIOSIS FOLLOWING SALPINGECTOMY. JOHN A. SAMPSON, *Am J Obst & Gynec* **16** 461, 1928

Sampson demonstrated that salpingectomies, as usually practiced, injure the endosalpinx, and the latter may subsequently invade the tubal stumps and the structures adherent to it. This was shown in thirty of thirty-six patients whose fallopian tubes had been operated on. Endometriosis grew out of the misplaced and traumatized tubal mucosa as sprouts or seedlings near the tubal stumps and invaded the uterine cornu. Endometriosis of the tissues of the broad ligament was continuous with the endometrial-like lesions on the median side of the ovary (three cases), or with the scar of the abdominal wall in two cases of ventrofixation of the uterus. The author believes that the ordinary surgical technic carelessly transplants tubal epithelium to other anatomic sites or within the incision. The misplaced tubal mucosa at times retains its original structure or assumes the structure and function of the uterine mucosa. The term endometriosis used for invasion by either tubal or uterine mucosa was admitted to be inadequate but was preferred to other names proposed by investigators of ectopic müllarian tissue.

A J KOBAK

CYCLICAL AND OTHER VARIATIONS IN THE TUBAL EPITHELIUM. E. NOVAK and H. S. EVERETT, *Am J Obst & Gynec* **16** 499, 1928

Novak and Everett show that the tubal epithelium exhibits definite cyclical changes comparable with those of the endometrium, but does not participate in the bleeding of the menstrual process. Two types of cells are chiefly concerned with this cycle. For example, the ciliated cells which reach the height of development during the interval period, and become smaller during the premenstruum, and the nonciliated or "secretory" cell which exhibits greatest development and activity in the premenstruum. During the menstrual phase the ciliated cells become smaller and the nonciliated cells empty their cytoplasmic contents. During the postmenstruum period, both types of cells are smallest but growth rapidly recurs up to the interval phase. A third type of cell designated as "Peg" cells are described, but their function and origin are rather obscure. In prepuberty, the epithelium is low, but both the ciliated and the nonciliated cells are present. The epithelium during the menopause remains high for a number of years. The corpus luteum was considered responsible for cyclic variation in the tubal epithelium similar to that evoked in the endometrium. The tubal epithelium in patients having an "essential" hyperplasia of the endometrium was studied in a limited number of patients. The epithelium in general was tall and rather narrow with a diminution of secretory activity of the nonciliated cells. This is to be expected since this hyperplasia is functional and based on an excess of follicle stimulus with diminished corpus luteum influence, whereas the cyclic changes were attributed to the physiologic response of the two chief types of cells to both the follicle and the corpus luteum.

A J KOBAK

STUDIES IN ACROMEGALY (FUGITIVE ACROMEGALY) PERCIVAL BAILEY and HARVEY CUSHING, *Am J Path* 4 545, 1928

That whereas a highly chromophilic type of adenoma, the cells of which are heavily laden with alpha granules characterizes outspoken acromegalic hyperpituitarism, and whereas an adenoma of purely chromophobe type with nongranular cells is commonly associated with adult hypopituitarism, there is an intermediary group of cases in which traces of these opposed symptoms have apparently been present from the outset and which are associated with a histologically distinctive adenoma with cells of fetal type having sparse, peripherally disposed granules. Since this intermediary syndrome is distinguishable clinically from the more common hypopituitary state by recognizable traces of hyperpituitarism, we find it convenient to refer to the disorder as fugitive acromegaly.

AUTHORS' SUMMARY

EXPERIMENTAL GLOMERULONEPHRITIS PRODUCED BY INTRARENAL TUBERCULIN REACTIONS ESMOND R LONG and LUCY L FINNER, *Am J Path* 4 571, 1928

The experiments described demonstrate that, by the injection of tuberculin into the kidneys of swine made sensitive to this substance by the presence of mild tuberculosis, it is possible to produce a diffuse inflammation of the kidneys that may properly be considered an acute glomerulonephritis. Moreover, this effect is the result of a true tuberculin reaction, as it does not occur following the perfusion of the kidney of a nontuberculous animal with tuberculin. We may therefore add the intrarenal tuberculin reaction to the intradermic, conjunctival, intratesticular and other anatomic varieties of tuberculin reaction previously described. The immediate reaction in the kidney is followed by a subsidence of acute manifestations, and absorption and proliferative organization of the exudate. Many of the glomeruli in this stage show the epithelial and endothelial stimulation and growth seen in a late "acute proliferative glomerulonephritis," or in a subacute glomerulonephritis. True epithelial crescents are occasionally seen. Atrophy of the tubules associated with the more severely injured glomeruli occurs. When the injury is bilateral, a moderate nitrogen retention develops. In the experiments recorded here, this was seen regularly in the tuberculous pigs which had been subjected to renal tuberculin perfusion, and never in the nontuberculous animals similarly treated. With the passage of several months following the intrarenal, or more specifically intraglomerular tuberculin reaction, almost complete restoration to an anatomic normal occurs, at least if very young pigs are used, as was the case in this experiment. As the animals grow and the kidneys develop to normal bulk, the glomeruli increase in size accordingly. The only persisting signs of the former acute inflammation are small hyaline areas which occasionally contain old pyknotic polymorphonuclear leukocytes. These are usually located at the point of vascular attachment of the tuft and capsule. Simultaneously with this anatomic healing, complete functional recovery also occurs, shown by a disappearance of nitrogen retention and return of the blood to normal. The question naturally arises whether or not the artificial production of the nephritis here described has any relation to the spontaneous development of nephritis in man. It will be recalled that the majority of adult human beings in urban groups are sensitive to tuberculin, and therefore carry within themselves the potentiality for the type of injury herein recorded. It is conceivable that during the period of activity of a tuberculous focus, tubercle bacillus protein could be taken up, as by phagocytic cells, from the debris of the lesion and excite changes of an allergic nature at a distant point such as a glomerulus of a kidney. It is unlikely, however, that any such dosage as used in the experiments described could be so absorbed. It is possible, on the other hand, that occasional and scattered glomerular lesions could arise in this way. However, it must be remembered that the tuberculin reaction is only one of a type. A considerable number of analogous forms of sensitization exist. While such reactions are in general protective against

the spread of the infection concerned, the act of protection itself may be destructive to the local tissue, and no initial distinction is made in the reaction to live bacteria or their dead specific protein. These facts, together with the experiments reported here, justify further work in this field.

AUTHORS' SUMMARY

THE PHAGOCYTIC ACTIVITY OF THE VASCULAR ENDOTHELIUM OF GRANULATION TISSUE F A MCJUNKIN, *Am J Path* **4** 587, 1928

Carbon is present in the vessel walls of granulation tissue after india ink has been injected intravenously and also to some extent at the site of subcutaneous injections of ink. The presence of this particulate matter within the cytoplasm of the endothelial cells can be explained only as a process of active phagocytosis. The phagocytic activity of these endothelial cells is identical with that of the Kupffer cells of the liver which have a comparable amount of cytoplasm.

AUTHOR'S SUMMARY

THE EFFECT OF FEEDING POTASSIUM IODIDE ON THE PROLIFERATIVE ACTIVITY OF THE THYROID GLAND IN GUINEA-PIGS JACOB RABINOVITCH, *Am J Path* **4** 601, 1928

A quantitative estimation of the proliferative activity of the thyroid gland has been carried out, by counting the number of mitoses present in the normal gland as well as in the glands of guinea-pigs fed with various quantities of potassium iodide during different periods of time. The number of mitoses found in thyroids obtained from animals fed with potassium iodide within the first three weeks after the beginning of the feeding is by far greater than that observed in the controls. The increase in the number of mitoses is only slight during the first ten days. It becomes very pronounced between the fifteenth and the twentieth day of the iodide feeding, and lessens again when feeding is continued for thirty days. Within the range of quantities of the substance used by us, larger doses of potassium iodide call forth greater proliferative activities of the thyroid epithelium than smaller doses. At the same time the colloid becomes slightly softer and the phagocytic activity within the colloid increases after potassium iodide has been fed for fifteen to twenty days, the epithelium, however, changes very little in height. At the end of the thirtieth day, the acini enlarge and become irregular, the colloid becomes watery and the epithelium flattens out, the number of phagocytes also diminishes. We attribute the flattening of the acinus epithelium, which is observed in the fifth week, to the pressure exerted on the epithelium by the increase in volume in the colloid resulting from the absorption of water at this period.

AUTHOR'S SUMMARY

CONGENITAL ATRESIA OF AORTIC RING N PHILPOTT, *Ann Int Med* **2** 422, 1928

Philpott describes the autopsy observations in the case of an infant who lived sixty-two hours after birth. On the day after delivery, cyanosis appeared and deepened progressively until death occurred. The administration of oxygen was without effect. There was no mitral opening. A direct communication between left and right auricles was established by means of a widely patent foramen ovale. There was complete atresia of the aortic ring. The ductus arteriosus was widely patent.

WALTER M SIMPSON

RELAPSING FEBRILE NODULAR NONSUPPURATIVE PANNICULITIS H A CHRISTIAN, *Arch Int Med* **42** 338, 1928

A case is reported in which there were irregularly distributed inflammatory nodules in the subcutaneous fat. Ten such attacks occurred in nine years. They were associated with fever up to 104 F, malaise, nausea and vomiting. His-

tologic study of the tissues showed edema and some atrophy of the subcutaneous fat, and infiltration largely by mononuclear types of cells, with occasional giant cells. Bacterial cultures of the affected tissues were negative. As the process healed, there was depression of the skin into the hollowed out places left by atrophy of the fat.

H R FISHBACK

PANCRATOGENOUS FATTY DIARRHEA T E H THAYSEN, Arch Int Med **42** 352, 1928

The case presented is one of fatty diarrhea of five years' duration, associated with chronic diffuse pancreatitis and stone in the pancreatic ducts. Azotorrhea was present to a marked degree, but not glycosuria. Previous workers have suggested the hypothesis that the pancreas passes an internal secretion into the blood, which is active in fat and protein metabolism.

H R FISHBACK

RELATIVE LYMPHOCYTOSIS IN HYPERTHYROIDISM V MENKIN, Arch Int Med **42** 419, 1928

In 100 cases of hyperthyroidism there was a relative lymphocytosis in 67 per cent. Of the group with exophthalmos, there was relative lymphocytosis in 80 per cent, and in these thyroidectomy restored the normal differential formula. This return to normal did not always occur in the patients with lymphocytosis and without exophthalmos.

H R FISHBACK

CHANGES IN THE FUNDUS OCULI AS AN INDEX TO ARTERIAL DISEASE S A AGATSTON, Arch Int Med **42** 455, 1928

Sclerosis of the arterioles of the kidney and brain cannot exist without a similar condition of the retinal arteries, and normal retinal vessels definitely exclude interstitial nephritis of the sclerotic type. Cases of nephritis on a basis of infection with considerable albuminuria may show a normal fundus or a neuroretinitis with little or no retinal vessel change. The extent of sclerosis of the retinal arteries is generally proportional to the changes in the kidneys, the height of the blood pressure and the nonprotein nitrogen of the blood. Patients with incipient hypertension may suffer from spasmodic contraction of arteries giving temporary blindness, angina or cerebral symptoms. Patients with vascular disease without hypertension are especially liable to thrombosis. Moderate changes of the retinal vessels recognized by the ophthalmoscope may not be found by microscopic study.

H R FISHBACK

SCLERODERMA AND CALCINOSIS R H DURHAM, Arch Int Med **42** 467, 1928

A review is given of scleroderma and calcinosis as to case reports, theories of pathogenesis and incidence. It is suggested that the two conditions together constitute a distinct pathologic entity.

H R FISHBACK

## Pathologic Chemistry and Physics

CHEMICAL CONTRASTS BETWEEN COLLAGENOUS AND RETICULAR CONNECTIVE TISSUE NATHAN CHANDLER FOOT, Am J Path **4** 525, 1928

In the connective tissue framework of the spleen in man, isolated by means of tryptic digestion, there are three main groups of fibrous substances—"collagen," elastin and reticulin. The first may be completely extracted by boiling water, leaving the white fibrous tissue incapable of taking specific collagen stains. The extract may be coagulated on slides by means of gentle heat and fixation in Zenker's fluid and a substance will be recovered that gives all the characteristic staining reactions of collagen and many of the precipitation reactions of gelatin. The elastin resists boiling water, and weak acid or alkaline solution. It may be digested



with pepsin and hydrochloric acid, 0.3 per cent (This was not mentioned in the body of the paper, it is given for the sake of completeness) The reticulin is composed of a mixture of at least three groups of substances: an alcohol-soluble group (lipins, largely impure lecithin), an alcohol-insoluble group made up of an argyrophil material that may come down as threads and a silver neutral background of amorphous matter that forms the bulk of the fraction, this may be digested fibers. After extracting these substances from the splenic framework, if alkali-digestion has not been carried too far, pale fibers that stain neither with silver nor fuchsin remain, these may be stained with eosin, picric acid or phosphotungstic acid hematoxylin, rose, yellow and reddish, respectively ("true collagen?") The staining reactions of the substance extracted with boiling water and those of commercial gelatin are not the same. Using the technic herein described, jellies are seldom produced. The argyrophil matter in the reticulin is best demonstrated after exposure to certain oxidizing agents, while reducing agents apparently inhibit impregnation. There is a possibility that the water-soluble "collagen" and the alkali-soluble "reticulin" constitute stiffening, strengthening or protective substances for the fibers of the connective tissue, they impregnate these evenly and may be extracted without destroying the fibers. The assumption that reticulin may be hydrolyzed to collagen is not unwarranted.

AUTHOR'S SUMMARY

STUDIES OF THE INHIBITORY ACTION OF AN EXTRACT OF PANCREAS UPON GLYCOLYSIS E. RONZONI, J. GLASER and D. P. BARR, *J. Biol. Chem.* **80** 309 and 331, 1928

A simplified method is described for extracting from pancreas the substance which has the property of inhibiting the normal course of glycolysis in muscle. The substance is not insulin. Its action appears to be directed toward a retardation of the formation of lactacidogen (hexose phosphate). Since the extract appears to have no effect on the glycolysis of cancer tissue, it is concluded that the mechanism of sugar breakdown in such tissue is different from that normally occurring in muscle.

ARTHUR LOCKE

SEASONAL VARIATIONS IN THE IODINE AND THYROXINE CONTENT OF THE THYROID GLAND E. C. KENDALL and D. G. SIMONSEN, *J. Biol. Chem.* **80** 357, 1928

The iodine content of the thyroid gland varies with the seasons, reaching a maximum during the warm weather of July and August and a minimum during the colder months of January and February. There appears to be a parallel but considerably less marked fluctuation in the thyroxine content of the gland. The iodine present as thyroxine represents less than 14 per cent of the total amount available. "It is impossible to explain the physiological activity of fresh or desiccated thyroid by the thyroxine which can be separated in crystalline form. Thyroxine appears to be an intermediate form of the active constituent of the thyroid."

ARTHUR LOCKE

DISTRIBUTION OF UNSATURATED FATTY ACIDS IN TISSUES W. R. BLOOR, *J. Biol. Chem.* **80** 443, 1928

The phospholipid concentration of an organic tissue would appear to be a direct index of its functional activity. It maintains a fair constancy throughout the growth of the organ (beef), reaches a maximum in the cerebral tissues and descending values in the liver, pancreas, kidney and lung, respectively. The phospholipids of these organs are constituted of approximately equal parts of lecithin and cephalin, suggesting the existence of an equimolecular equilibrium or combination between the two substances.

ARTHUR LOCKE

THE UROBILIN CONTENT OF NORMAL HUMAN BLOOD M A BLANKENHORN,  
J Biol Chem **80** 477, 1928

Urobilin zinc acetate has the remarkable and specific property of becoming strongly fluorescent on proper illumination. The property has been made the basis of the Schlesinger test for the presence of urobilin in biologic material and of the Lutz test for the presence of zinc. The Schlesinger test permits the detection of concentrations of urobilin as minute as 0.000,048 mg per cubic centimeter, but can be used to advantage only when the solutions to be examined are perfectly clear. The illumination of cloudy solutions produces a Tyndallization, which tends to obscure and nullify the looked-for fluorescence. Blankenhorn's procedure is to permit from 2 to 3 cc of the specimen (clear blood serum) to become coagulated on shaking with 0.5 Gm of powdered zinc acetate. After further shaking with 3 volumes of absolute alcohol, the well stoppered specimen is held in the icebox for twenty-four hours and then strongly centrifugated. The fluorescent capacity of the clear supernatant fluid is compared in a specially constructed chamber with that of a known dilution of acriflavine. (The use of a light filter, as employed by Lutz [*J Indust Hyg* **7** 273, 1925] to remove that part of the spectrum responsible for the Tyndallization, while retaining the part essential for the production of fluorescence, appears not to have been attempted.) The urobilin content of normal human blood, as indicated by an analysis of 128 varied specimens, appears to be approximately 0.0028 mg per cubic centimeter.

ARTHUR LOCKE

THE ACID-BASE COMPOSITION OF GASTRIC SECRETIONS, PANCREATIC JUICE  
AND BILE JAMES L GAMBLE and MONROE A McIVER, J Exper Med **48**  
837 and 849, 1928

The chief inorganic factors in secretions obtained from isolated pouches constructed in the fundus and in the pyloric antrum of the cat's stomach were found to be chloride ion and fixed base. In a series of samples obtained from the fundic pouch, chloride ion was approximately stationary at 165 cc tenth-normal per hundred cubic centimeters. During digestion of food in the stomach, secretions from the pouch contained fixed base in amounts varying considerably from an average of 47 cc tenth-normal per hundred cubic centimeters. Material allowed to remain in the pouch after the completion of the digestion of food in the stomach showed an increasing content of fixed base, to as much as 140 cc tenth-normal per hundred cubic centimeters. A stationary total ionic content of secretions of the fundus is thus seen to be sustained by the chloride ion concentration, and changes in hydrogen ion concentration to be caused by variation of fixed base. The differing amounts of fixed base found are regarded as probably due to admixture of a mucous secretion with the juice from the fundic glands. The alkaline secretion taken from a pyloric pouch contained fixed base in excess of chloride ion. Variation of fixed base in the secretions from the fundic pouch were found to be referable to change in sodium content, the smaller factor, potassium, remaining approximately constant at about the value found in material from the pyloric pouch. This suggests that the mucous secretion of the fundus has the same composition as that produced by the pyloric antrum. These data serve to explain the extensive withdrawal of fixed base, as well as of chloride ion, from the blood plasma in the presence of circumstances causing a continued loss of stomach secretions.

Pancreatic juice contains fixed base at approximately the concentration found in the blood plasma. Chloride ion is present in concentrations varying from one-fourth to one-half the fixed base value and the remainder of the acid equivalence is composed of bicarbonate ion. Fixed base being a nearly stationary factor, variation of bicarbonate and thereby of alkalinity is referable to change in the concentration of chloride ion. In bile, as delivered by the liver, both the fixed base and the chloride ion values correspond closely with their respective concentrations in blood plasma. In gallbladder bile, however, the concentration of fixed base is, roughly, double that in hepatic duct bile, and chloride ion has been almost entirely

removed From these data, it may be inferred that loss of digestive secretions entering the duodenum will, in the absence of replacement of the materials contained, cause dehydration of the blood plasma and reduction of the plasma bicarbonate

AUTHORS' SUMMARY

CHANGES IN FLUIDS OF BODY FROM LOSS OF THE EXTERNAL SECRETION OF THE PANCREAS JAMES L GAMBLE and MONROE A McIVER, J Exper Med 48 859, 1928

The following explanation of the effects of continued loss of the external secretion of the pancreas may be offered The underlying event is a steadily increasing deficit of sodium and of chloride ion due to the large requirement for these electrolytes in the construction of pancreatic juice In consequence there is continued loss of water, chiefly from the body fluids in which sodium and chloride ion are large factors of total ionic content, viz, interstitial fluids and the blood plasma During about two thirds of the survival period, the volume and composition of the blood plasma remain approximately normal, the losses of water, sodium and chloride ion being replaced at the expense of interstitial fluids Reduction of the volume of these fluids is indicated by loss of body weight, beginning directly after establishment of the pancreatic fistula Ultimately, reduction of the volume of the plasma begins and, as it progresses, serious symptoms develop and death occurs, unless water, sodium and chloride ion are abundantly replaced Owing to the relatively greater loss of sodium than of chloride ion in pancreatic juice, reduction of bicarbonate ion concentration in the plasma tends to occur The death of the organism may be simply and reasonably explained as the result of progressive impairment of the function of the blood by the physical changes, dehydration and acidosis, produced in the plasma by the continued loss of sodium and of chloride ion in the pancreatic juice

AUTHORS' SUMMARY

ESTIMATIONS OF THE HYDROGEN ION CONCENTRATION OF THE URINE F MAINZER, Klin Wchnschr 8 109, 1929

Urine taken with the exclusion of air at 38 C is best suited for the determination of the hydrogen ion concentration This method is practicable with single specimens, but difficult with collections of many hours For collected samples, the measurement of the hydrogen ion concentration with a carbon dioxide tension of 40 mm mercury at room temperature is satisfactory On this basis is the advantage of the method mentioned over measurements disregarding the carbon dioxide tension

ARTHUR'S SUMMARY

## Microbiology and Parasitology

RICKETTSIA IN MOSQUITOES (*Aedes aegypti*) INFECTED WITH THE VIRUS OF DENGUE FEVER ANDREW WATSON SELLARDS and JOSEPH F SILER, Am J Trop Med 8 279, 1928

Masses of *Rickettsia* were frequently found in mosquitoes (*Aedes aegypti*) which were known to be infected with the virus of dengue fever No *Rickettsia* was found in control mosquitoes

A contaminating protozoon resembling developmental forms of *Lankesteria culicis* occurred in some of the control mosquitoes This contaminating organism can, under certain conditions, offer some confusion in the study of *Rickettsia* in smears

AUTHORS' SUMMARY

THE FLAGELLATED PROTOZOA OF THE INTESTINE KENNETH N LYNCH, Am J Trop Med 8 345, 1928

There was no evidence that diarrhea was related in any way to the presence of *Trichomonas hominis* or *Chilomastix mesnili* There was no evidence that constipation was related to the presence of *Trichomonas*, but constipation was a

common habit of the persons harboring *Chilomastix*. Among 240 unwell persons harboring intestinal flagellates, there was no case of arthritis deformans. The presence of *Trichomonas hominis* appears to be more related to rural life and to warm climates, while the presence of *Chilomastix mesnili* appears to be more related to city life but relatively unrelated to climate. Infestation with *Giardia intestinalis* was more frequent in early life, *Chilomastix mesnili*, in later life, while the age of the person had apparently no relation to the presence of *Trichomonas hominis*. A state of lowered acidity of the stomach appeared to be favorable to the presence of *Chilomastix* but of no relation to *Trichomonas*. The observation is made that a clinical diagnosis of chronic cholecystitis was recorded in about twice as many of the carriers of *Trichomonas* and *Chilomastix* as in the flagellate-free

AUTHOR'S SUMMARY

THE STREPTOCOCCUS, AN ALLY OF SMALLPOX. J. G. CUMMING, Contributions to Medical Science Dedicated to A. S. Warthin, Ann Arbor, George Wahr, 1927, p. 283

In a series of twenty successive cases in patients with smallpox admitted to the Isolation Hospital, Washington, D. C., Cumming found eight persons who were tonsillar carriers of hemolytic streptococci. In the group of twenty patients, there were six deaths, all among the streptococcus carriers. In all the fatal cases, hemolytic streptococci were isolated, not only from the throat, but also from the blood stream within forty-eight hours before death or from the heart's blood immediately after death, or from both sources.

Cumming concludes that in fatal cases of smallpox the immediate cause of death is a septicemia caused by hemolytic streptococcus, in which the hemolytic streptococcus is activated to its maximum virulence by the smallpox virus.

WALTER M. SIMPSON

THE REACTION OF THE OMENTUM TO GERM SUBSTANCE. W. T. VAUGHAN, Contributions to Medical Science Dedicated to A. S. Warthin, Ann Arbor, George Wahr, 1927, p. 503

In a study of the reaction of the omentum to foreign material implanted within the peritoneal cavity, Vaughan inoculated each of a series of guinea-pigs with 10 mg. of dead tubercle bacillus germ substance in 1 cc. of physiologic solution of sodium chloride. Within twenty-four hours, the omentum had gathered up practically all of the material, and it was found closely adherent to the omental surface. In its reaction, the omentum often becomes adherent to adjacent structures. In control animals inoculated with Tobler bacillus germ substance, bone ash, lycopodium spores and animal charcoal, the injected material was invariably found attached only to the omentum.

Microscopically, in animals killed twenty-four hours after inoculation, the tubercle bacillus germ substance is found attached to the surface by fibrinous exudate or incorporated in the tissues just beneath the surface. The foreign material is surrounded by a heavy accumulation of leukocytes and wandering cells with large, clear, pale-staining nuclei, and a few lymphocytes.

At the end of a week, the clumps of germ substance are surrounded by whorls of rather dense connective tissue fibrils. The wandering cells and polymorphonuclear leukocytes persist in great numbers. The larger the foreign body mass the less extensive is the proliferation of the connective tissue, and actual suppuration occurs.

After thirteen days, the small masses of foreign bodies have been practically entirely removed, and the site of each mass is replaced by a dense connective tissue whorl. The wandering cells now clearly predominate over the leukocytes. The connective tissue reaction to the larger masses is well advanced.

After thirty-three days, the reparative changes are quantitatively greater. There was evidence that other organs with peritoneal covering aid in the removal of the particulate matter.

The reaction of the omentum to foreign body substance does not differ essentially from such reaction in other tissues the functions of which are not so clearly protective. The tendency toward encapsulation may be somewhat more pronounced, thus accounting for the occasional development of omental cysts, not embryonic in origin

WALTER M. SIMPSON

VIRUS III ENCEPHALITIS THOMAS M. RIVERS and FRED W. STEWART, J  
Exper Med 48 603, 1928

Virus III, an active, filtrable agent indigenous to rabbits, under experimental conditions, produces, in addition to lesions in the cornea, skin and tests, an encephalitis which is at times fairly similar to that induced by herpetic virus. Virus III and herpetic virus, however, are not immunologically related

AUTHORS' SUMMARY

CHEMOTHERAPY IN EXPERIMENTAL OROYA INFECTION HIDEYO NOGUCHI,  
J Exper Med 48 619, 1928

The therapeutic effect of several antiparasitic chemicals on experimental verruga peruana is described. The drugs were administered by intravenous injection according as the nodules were already developed to an approximate maximum, or were still in the active period of growth. The effect of the drugs was different under the two circumstances of their administration. When they were given after the maturity of the nodules, they hastened the regressive process, but when given during active growth of the lesions, no action was detected. *Bartonella bacilliformis* in culture is acted on injuriously by a number of the chemicals employed in the therapeutic tests, the most active being formaldehyde and neutroflavine

AUTHOR'S SUMMARY

A PARATYPHOID INFECTION IN GUINEA-PIGS JOHN B. NELSON, J Exper Med  
48 647, 1928

A group of 105 breeders and 36 unweaned guinea-pigs was tested to determine the extent of specific fecal excretion and the proportion of serum reactors in a population naturally infected with two types of *B. paratyphi*. The second more recent type of organisms was isolated from the feces of three breeders and three young guinea-pigs. No carriers of the first type were detected. Eighty-six per cent of the breeders and 72 per cent of the unweaned guinea-pigs agglutinated the second type of *B. paratyphi* in dilutions ranging from 1:10 through 1:640. Thirteen per cent of the breeders and 28 per cent of the unweaned young guinea-pigs agglutinated the initial type. There was a cross or double agglutination in most instances. The serologic observations roughly reflected the distribution of the two types as indicated by the mortality rate of the population at large. Fifty breeders selected on the basis of agglutination and fecal examination and therefore supposedly free from infection were segregated and kept under close observation. Both types of *B. paratyphi* subsequently appeared in the group. During this time, carriers were discovered by others in the department among the stock guinea-pigs used for other experiments in that cultures of the entire spleen were positive in perhaps from 5 to 10 per cent of the guinea-pigs so used.

AUTHOR'S SUMMARY

EXPERIMENTAL PNEUMONIA IN GUINEA-PIGS JULIA T. PARKER and ALWIN M.  
PAPPENHEIMER, J Exper Med 48 695, 1928

Anaerobic autolysates of pneumococci, prepared according to the method described, are highly toxic for guinea-pigs when injected intratracheally in a dosage of 0.2 cc. Death occurs either within a few hours (36 per cent) or within three days. In the early deaths there is intense hemorrhagic edema of the lungs with beginning inflammatory reaction, in animals surviving for eighteen hours or longer extensive areas of pneumonia are produced. The intratracheal injection of

virulent living pneumococci is followed by transient slight lesion with recovery, or by later death from septicemia without pneumonic lesions. The addition of a sublethal dose of toxic autolysate to living pneumococci alters the reaction of the animal, so that an extensive pneumonia develops associated with unrestrained multiplication of the organism

AUTHORS' SUMMARY

BACTERIOPHAGE OF PSYCHROPHILIC ORGANISM A LAWRENCE ELDER and FRED W TANNER, J Infect Dis **43** 403, 1928

A bacteriophage active for a psychrophil has been obtained. The specificity of the bacteriophage was fairly pronounced, as shown by the fact that it was not readily active on any of fifty-nine other psychrophils studied. Macroscopic observations of the lytic action confirmed all the usual characteristics of bacteriophagy

AUTHORS' SUMMARY

MUCOSUS ORGANISM FROM SUPPURATIVE LESIONS OF RAT ON DIET DEFICIENT IN VITAMIN A WILLIAM L BRADFORD, J Infect Dis **43** 407, 1928

By aerobic cultures from the suppurative terminal lesions in the white rat on a diet deficient in vitamin A, an encapsulated bacillus of the mucosus encapsulated group has been isolated in about one-half the cases. From fifty rats on A-deficient diet, representing three different stocks twenty-one strains were isolated. In thirteen normal rats three rats on B-deficient diets and nine rats on D-deficient diets, all without obvious infections, cultures from the ears and nose failed to reveal the organism. It was recovered once in a series of ten wild (brown) rats from the nose. Although obviously more frequently present in the suppurative conditions of the animal on an A-deficient diet, it is probably a secondary invader of mucosa of the respiratory tract, made suitable for its invasion by the dietary deficiency. The organism has been found to be suitable for use in a study of the relationship between vitamin deficiencies in diet and resistance to infection which will be reported

AUTHOR'S SUMMARY

ETIOLOGY OF DERMATITIS OF EXPERIMENTAL PELLAGRA IN RATS W D SALMON, I M HAYS and N R GUERRANT, J Infect Dis **43** 426, 1928

The external symptoms of experimental pellagra of the rat are alopecia, dermatitis, stomatitis, ophthalmia and arthritis, and usually cachexia. The internal lesions of advanced cases are hemorrhagic gastro-enteritis, atrophy of the spleen, fatty infiltration or degeneration of the liver, cloudy swelling of the kidneys and often cystitis. There is a relation between the character of the diet and the occurrence of the syndrome. A mild dermatitis has been found among mature rats receiving a diet which is adequate for excellent growth and reproduction. The severe form has been produced only on restricted diets.

A gram-positive coccus has been found constantly associated with the disease. This organism has been isolated (often in pure culture) from skin lesions, arthritic lesions, parenchymatous organs and walls of the intestines of pellagrous rats. With two exceptions the organism has not been obtained from the blood stream. The organism has been fed to rats and the characteristic lesions, from which the organism has been recovered, have been produced.

Concentrates of a protective principle (P-P factor) which cure or prevent the occurrence of the disease have been prepared from *Pueraria thumbergiana*. A relatively low concentration of these preparations in nutrient broth inhibits the growth of the causative organism.

AUTHORS' SUMMARY

OBSERVATIONS ON SNAFFLES IN RABBITS F RENE VAN DE CARR and KATHLEEN J KILGARIFF, J Infect Dis **43** 442, 1928

A systemic response of the rabbit to infection of the respiratory tract with *B. leptosepticum* and *B. bronchisepticus* was demonstrated by serologic and allergic

reactions The serologic and allergic reactions correlate with the bacteriologic observations to a high degree the allergic reactions to a higher degree than the serologic reactions The allergic reactions were apparently specific They may prove to be a simple, more direct method of detecting infected or immune rabbits

*B. lepi-septicum* or *B. bronchisepticus*, or both, were demonstrated in every case of clinical snuffles in this study *B. lepi-septicum* or *B. bronchisepticus*, or both together, may be responsible for snuffles in rabbits In manifestations of acute snuffles, such as bronchopneumonia, pleurisy, pericarditis and septicemia, *B. lepi-septicum* alone was demonstrable

A 2 per cent solution of silver nitrate was found to be useful in separating the carriers from the uninfected animals in a group of clinically healthy rabbits

## AUTHORS' SUMMARY

THE PROTEUS HEMOLYSIN JOHN F. NORTON, ELIZABETH VERDER and CATHERINE RIDGWAY, J. Infect. Dis. **43** 458, 1928

The production of an agent which is lytic for red blood cells is characteristic of the proteus group of bacteria The agent is heat labile, is formed during the first few hours of growth in a culture, is rapidly destroyed by phenol disinfectants, is absorbed by a Berkefeld N filter and is neutralized by both homologous and heterologous antisera

## AUTHORS' SUMMARY

THERMOPHILIC BACTERIA IN CANNED FOODS MYRILE SHAW, J. Infect. Dis. **43** 461, 1928

Twenty-three strains of obligate thermophiles were isolated from sixty-five cans of fruits and vegetables, and classified in two groups Twenty-one were so nearly identical as to be considered of the same species, all but three of which were obtained from corn and peas which were "flat sours," as indicated by the hydrogen ion concentration This would indicate a fairly homogeneous group responsible for this type of spoilage Two cultures were obtained from swelled cans of pumpkin These cultures seemed unlike the majority of those in the group of twenty and unlike any previously described in the literature They were considered a new species and named *Bacillus pepo*

Facultative thermophiles were not found

Two variations of standard technic were devised and used in the determination of reactions which with the use of standard methods, were weak or indefinite These were variations in the use of potato slants and starch agar plates

## AUTHOR'S SUMMARY

RELATIONSHIP BETWEEN CHRONIC INTESTINAL STASIS AND ANEMIA PAUL R. CANNON, J. Infect. Dis. **43** 480, 1928

Chronic intestinal obstruction with resulting stasis in the ileum has been produced in forty-five albino rats Diets favoring the development of proteolytic bacteria have been fed to such animals in an attempt to determine whether or not hemolytic substances may be formed and absorbed and thus lead to an anemia

In most instances, no significant anemia occurred, whenever it did develop under these conditions, it was possible to demonstrate evidences of a concomitant acute infection

Chronic ileal stasis in the albino rat, with a proteolytic intestinal flora, may be present for several weeks with no significant increase in blood destruction, provided an intercurrent infection does not supervene Consequently, in experimental animals, one cannot conclude that an anemia is due to the absorption of hemolytic substances from the lumen of the bowel until all evidences of acute infection have been eliminated by bacteriologic and histologic procedures

## AUTHOR'S SUMMARY

NEISSERIA SUBFLAVA (BERGEY) MENINGITIS IN AN INFANT HARRIET BENSON, ROSE BRENNWASSER and DOROTHY D'ANDREA, J Infect Dis 43 516, 1928

This report describes the clinical progress, the bacteriology and the results of the postmortem examination, including an extended account of the alterations in the brain, of a chronic meningitis in a child 7 months of age from whose spinal fluid *N. subflava* was repeatedly isolated. Anatomically, there was a marked internal hydrocephalus and a pressure displacement by a circumscribed abscess of the tissues of the inferior portion of the cerebellum and the upper part of the spinal cord.

The prolonged mild course of the illness continuing for about three months was a notable clinical feature. Gram-negative diplococci observed in stained preparations of spinal fluid commonly are considered to be meningococci. This conclusion cannot be safely made without careful study of the organisms in culture mediums and by serologic tests. Although the members of the flava group as well as *N. catarrhalis* and *N. sicca* have little pathogenicity in human hosts, they seem to be able to produce disease in susceptible persons.

AUTHORS' SUMMARY

SPONTANEOUS TUBERCULOSIS IN RABBITS MALCOLM J HARRIS and ELLIOTT R SALLEBY, J Infect Dis 43 554, 1928

Two cases of tuberculosis in rabbits are described. Besides the rarity of the disease in rabbits the most interesting feature was the atypical gross and histologic appearance of the nodules in one of the animals. The distribution on the serous layers and the atypical cells suggested a neoplasm of the endothelioma type. Continued passage through other rabbits resulted in more nearly typical nodules. Tubercle bacilli were demonstrated in both cases.

AUTHORS' SUMMARY

GLUCOSE INHIBITION OF EXTRACELLULAR TOXIN-PRODUCING ENZYMES OF CLOSTRIDIUM BOTULINUM C N STARK, J M SHERMAN and PAULINE STARK, J Infect Dis 43 566, 1928

It is shown that when *Clostridium botulinum* is grown in a medium containing dextrose there results an inhibition of the production of the enzymes responsible for the extracellular formation of toxin. It is also noted that the toxin produced in dextrose broth is more stable than that formed in the same medium without the carbohydrate.

AUTHORS' SUMMARY

DESTRUCTION OF DIPHTHERIA TOXIN BY BACTERIA C N STARK, J M SHERMAN and PAULINE STARK, J Infect Dis 43 569, 1928

It has been shown that several bacteria have the power to destroy diphtheria toxin when grown in its presence. The data reported show this to be true of *Bacterium coli*, *Bacillus cereus*, *Proteus vulgaris*, *Pseudomonas pyocyaneus* and *Clostridium sporogenes*. Especially active destruction was caused by *Clostridium sporogenes*.

AUTHORS' SUMMARY

INCIDENCE OF PFEIFFER'S BACILLUS IN THROATS DURING EPIDEMIC AND INTEREPIDEMIC PERIODS IN CHICAGO JANET M BOURN, J Prev Med 2 441, 1928

Pfeiffer's bacillus was found with relative frequency in normal throats during interepidemic times. During one period marked by an unusual number of acute infections of the respiratory tract, the incidence of this organism in persons with normal throats was considerably increased. In cultures from the throat in cases of lobar and bronchopneumonia and pulmonary tuberculosis, the Pfeiffer bacillus was found much more frequently than in cultures from normal throats. In persons suffering with colds, sore throats or some mild irritation of the respiratory



mucosa, the incidence of the bacillus was slightly higher than that observed in persons with normal throats. The Pfeiffer bacillus was found in normal throats during interepidemic periods in the same proportion as it was found in association with the diseases of childhood

AUTHOR'S SUMMARY

EFFECT OF HEAT-KILLED CULTURES OF *SALMONELLA ACETICAE* IN MONKEYS AND OTHER ANIMALS. GAIL M. DACK, P. and H. HARMON and IRENE E. JARRA, J. Prev. Med. 2: 461, 1928

Monkeys, rabbits, dogs and cats fed with heat-killed cultures of *S. aceticae* failed to show the characteristic gastro-intestinal disturbances present in man in paratyphoid intoxication

AUTHORS' SUMMARY

UNSUCCESSFUL ATTEMPT TO PRODUCE SALMONELLA INTOXICATION IN MAN. GAIL M. DACK, WILLIAM E. CARY and PAUL H. HARMON, J. Prev. Med. 2: 479, 1928

Heat-killed dextrose-broth beef-heart cultures and filtrates of five strains of *Salmonella aceticae* and four strains of *Salmonella enteritidis*, when fed in large amounts to twenty-four adults on an empty stomach, failed to produce any symptoms, although the same materials produce symptoms and death when injected intravenously into rabbits in amounts of from 0.5 to 2 cc. No agglutinins for homologous strains were present in the serums of these subjects ten days after feeding

AUTHORS' SUMMARY

THE CULTURE OF THE SPIROCHETE OF RELAPSING FEVER. MARIO LAPIDARI and ILLÈNE SPARROW, Arch. Inst. Pasteur de Tunis 17: 191, 1928

The Ungeremman medium in which inactivated rabbit serum with Ringer's solution was tubed in long narrow tubes containing 1 cc. of coagulated egg albumin, the final product being covered with petrolatum, was found by the authors to be the best type of medium for cultures of the spirochetes of relapsing fever. They found that Huttley's tryptic digest broth (horse meat, digested with Cole and Onslow pancreatic extract), substituted for Ringer's solution improved the medium.

A detailed study of cultures demonstrated the possibility of serial transfer in a large number of cases. It was also observed that the material was at times infectious when no spirochetes could be found. This proof of existence of an invisible infectious agent, coupled with the statistical observations on the latent periods in the test tube cultures wherein potential spirochetes existed, leads the authors to suggest that they may have observed in vitro the existence of cyclic stages in the spirochete part of which are invisible, such as Nicolle believes to occur in man in relapsing fever.

M. S. MARSHALL

MYCETOMA OF THE THIGH DUE TO A TRICHOMYCETOSIS, *NOCARDIA NICOLLEI* N. SP. P. DRIANOI, Arch. Inst. Pasteur de Tunis 17: 257, 1928

A Moroccan adult was infected on the thigh with this fungus, considered to be a new species. The lesion, when first seen, dated back eleven years, when an inguinal adenitis developed which later spread. The right thigh showed marked tumefaction, the tissues being edematous with a dense infiltration. Covering a large area below the inguinal region were numerous hemispherical or elongated raised nodules of considerable size, giving the impression of cold abscesses. The contents of these lesions when first opened were serous, then bloody and serous and finally frankly bloody. The fluid contained numerous yellowish granules, varying in size. There were unquestionably metastases in other parts of the body.

A detailed description of the culture isolated from the granules and a photograph of the case are included in the article.

M. S. MARSHALL

THE HEAT TREATMENT OF STREPTOCOCCUS INFECTIONS B MENDEL, F STRELITZ and M BAUCH, *Klin Wchnschr* 7 1899, 1928

In vitro experiments with three strains of streptococci demonstrated that temperatures between 40.5 C for twenty-four hours and 48 C for fifteen minutes altered the organisms so that ten times the lethal dose was not regularly fatal in mice, and only with 100 times the lethal doses were all the animals killed. Rats into which injections of lethal doses of streptococci were made and kept at 41.5 C for eight hours lived, control animals died regularly. Treatment with heat for streptococcus infections is recommended on the basis of these results.

E F HIRSCH

AGRANULOCYTOSIS W SCHULTZ, *München med Wchnschr* 75 1667, 1928

Schultz summarizes the reports and new features recorded since his original publication. He restates the symptoms, the changes in tissues, the prognosis and the therapy. A specific causal agent has not been established.

E F HIRSCH

PATHOLOGIC ANATOMY OF TUBERCULOSIS OF THE MESENTERIC GLANDS M BOCK, *Ztschr f Tuberk* 52 30, 1928

In all cases of chronic tuberculosis of the mesenteric glands, there are inflammatory changes in the capsule of the gland, in the surrounding tissue and in the peritoneum, which is in direct contact with the glands. These alterations are partly tuberculous and partly nonspecific. The inflammatory alterations of the peritoneum and of the mesentery cause pain on pressure, diarrhea, constipation and increased mucous secretion.

MAX PINNER

THE BLOOD PICTURE IN TUBERCULOSIS IN CHILDHOOD L HINDERSIN, *Ztschr f Tuberk* 52 34, 1928

Hematologic alterations occur on small stimuli. The blood picture is therefore, if critically applied, of great significance in the therapeutic indication, but its prognostic significance extends only over short periods of time.

MAX PINNER

HOHN'S METHOD OF ISOLATING TUBERCLE BACILLI W ROLOFF, *Ztschr f Tuberk* 52 153, 1928

By Hohn's method it was possible to demonstrate the presence of tubercle bacilli in the sputum in twenty microscopically negative specimens. This method is nearly as reliable as animal inoculation and is much simpler.

MAX PINNER

## Immunology

THE DETERMINATION OF RATE OF HEMOLYSIS BY THE MEASUREMENT OF LIGHT TRANSMISSION H D KESTEN and T F ZUCKER, *Am J Physiol* 87 263, 1928

By the use of a photo-electric cell, calibrated for its purpose by means of blood suspensions of known hemolysis, the writers devised a means of determining the rate of hemolysis. Certain spontaneous changes in light transmission through dilute blood suspensions are discussed.

H E EGGERS

SAPONIN HEMOLYSIS OF HUMAN BLOOD H D KESTEN and T F ZUCKER, *Am J Physiol* 87 274, 1928

By means of the photo-electric method previously described, the writers studied the rate of saponin hemolysis of normal blood, as well as of blood from

anemic patients The latter hemolyzed more slowly than the normal The effects of temperature, red cell concentration and saponin concentration are discussed

H E EGGERS

SAPONIN HEMOLYSIS OF RETICULOCYTE-CONTAINING BLOOD T F ZUCKER and H D KESTEN, *Am J Physiol* **87** 280, 1928

In rabbits in which there had been induced marked secondary anemia by repeated bleeding, the saponin hemolysis rate was determined by the writers' photo-electric method, for the entire blood, and for the separate portions with high and low reticulocyte content In reticulocyte-containing blood the hemolysis rate was found to be at first faster, then slower, than that of normal blood Rapid blood regeneration was not found to result in the production of even a relatively homogenous group of more resistant cells

H E EGGERS

AN IMMUNE PHENOMENON IN EXPERIMENTAL RELAPSING FEVER HENRY EDMUND MELENEY, *J Exper Med* **48** 805, 1928

In five splenectomized squirrels and chipmunks that were reinoculated with a strain of *Spirochaeta recurrentis* which had previously been present in their blood, the first attack was entirely suppressed because the animals were immune to the strain of spirochetes inoculated, but after the interval which usually occurred between attacks, a relapse ensued, in which the strain of spirochetes present in the blood was different from the strain inoculated

AUTHOR'S SUMMARY

FLAGELLAR AND SOMATIC AGGLUTINATION JOHN B NELSON, *J Exper Med* **48** 811 and 825, 1928

Whole, shaken and heated suspensions of two *Salmonella* species were compared as to agglutinability, absorptive capacity and antigenic properties The results were in general agreement with the flagellar antigen concept of Smith and Reagh The removal of flagella by shaking or heating (100 C) resulted in altered agglutinability manifested by failure to give a floccular reaction with "whole" antiserum The deflagellated bacteria were able to absorb some flocculating agglutinin from that serum They were unable, however, to produce flocculating agglutinin on injection in rabbits Untreated, shaken and heated suspensions of a nonmotile bacterium (*Staphylococcus*) showed no differences with respect to agglutinability or absorptive capacity Soluble precipitable material was found present in small amount in culture filtrates of the motile bacteria and in greater concentration in filtrates of heated suspensions The bulk of the soluble material was of somatic origin and was not appreciably increased by the presence of flagella It was possible, however, to demonstrate soluble material in heated flagella suspensions The relation of such soluble substances to floccular agglutination and the production of flocculating agglutinin as suggested by Hadlev is discussed

It was shown that flocculating (flagellar) agglutinin and granulating (somatic) agglutinin display certain differences with respect to their removal from sensitized bacteria (*B paratyphi*) A 5 per cent solution of sodium chloride added to sedimented, sensitized bacteria followed by heating to 60 C for one hour removed approximately 50 per cent of the combined agglutinin There was little or no removal of granulating agglutinin either from the sensitized motile bacteria or from a sensitized nonmotile organism (*Staphylococcus*) Evidence was presented that the agglutinin removal was not dependent solely on disintegration of flagella by the conditions of extraction with a subsequent freeing of antibody

AUTHOR'S SUMMARY

THE PULMONARY CIRCULATION IN THE GUINEA-PIG DURING ANAPHYLACTIC SHOCK STEPHEN WENT and CECIL K DRINKER, J Exper Med **49** 21, 1929

Sheep serum in doses below 0.3 cc intravenously produces no pulmonary vasoconstriction in the guinea-pig. Guinea-pigs have consequently been sensitized with this substance and anaphylactic shock produced by doses of 0.1 and 0.2 cc. Pressure in the pulmonary artery has been measured by the method of Drinker and West and recorded photographically in a new and convenient manner. At an early stage in anaphylactic shock the pulmonary arterial pressure falls markedly, and this fall seems to precede the appearance of bronchiolar obstruction. The fall in pulmonary blood pressure in anaphylactic shock is in marked contrast to the rise in pressure resulting from intravenous injection of toxic foreign protein, such as horse serum.

AUTHOR'S SUMMARY

HYPERSENSITIVENESS TO DIPHTHERIA BACILLI JAMES M NEILL and WILLIAM L FLEMING, J Exper Med **49** 33, 1929

The paper describes an "immediate" skin reaction to derivatives of the diphtheria bacillus which is shown to be distinct from the "delayed" or "pseudoreaction" commonly seen in Schick tests on adults. The "immediate" reaction was passively transferred to local areas of the skin of other people.

AUTHOR'S SUMMARY

SENSITIZING PROPERTIES OF THE BACTERIOPHAGE CLAUS W JUNGBLUT and EDWIN W SCHULTZ, J Exper Med **49** 127, 1929

Marked specific contractions of the uterine horns of guinea-pigs, actively sensitized, to phage-lysed Flexner bacilli or to colon bacilli, lysed by the same bacteriophage, occurred on testing either series for anaphylaxis with the homologous phage lysates. These reactions, however, were not due to an antigenic function of the bacteriophage itself, because no reaction whatsoever occurred when the same bacteriophage, propagated on the heterologous organisms, was substituted in the anaphylactic test. Specific uterine reactions of marked intensity were obtained in guinea-pigs, actively sensitized to intact or autolyzed Flexner or colon bacilli, respectively, by testing either series for anaphylaxis with homologous, phage-free bacterial antigens. No reaction occurred by testing the uterine strips of animals, sensitized to intact or autolyzed bacilli (either Flexner or coli), for anaphylaxis with homologous phage lysates and, vice versa, there was no contraction of uterine strips sensitized to phage lysates on contact with homologous bacterial autolysates. The observations made in this paper suggest that a new and immunologically distinct antigenic complex arises from the bacterial protein after lysis of the organisms by the bacteriophage.

AUTHOR'S SUMMARY

RELATIONSHIP BETWEEN A VARIETY OF SACCHAROMYCES CEREVISIAE AND THE TYPE II VARIETY OF DIPLOCOCCUS PNEUMONIAE (PNEUMOCOCCUS) JOHN Y SUGG and JAMES M NEILL, J Exper Med **49** 183, 1929

The paper reports evidence of an immunologic relationship between one variety of *Saccharomyces cerevisiae* and the type II variety of *Diplococcus pneumoniae* (pneumococcus). The most convincing data consisted of the reactions of the type II bacteria with potent antiyeast serum which agglutinated, and protected mice against these pneumococci as well as the average antiserum obtained by immunization of rabbits with type II bacteria themselves. The reactivity of the antiyeast serum is strictly specific to the type II variety of pneumococcus in the sense that it is entirely devoid of antibodies reactive with type I or III. The results of absorption experiments with both the antiyeast (rabbit) serum and the anti-type II (horse) serum were the same as those usually obtained in analogous experiments with immunologically related, but not identical, kinds of bacteria. The

immunologic relationship of the yeast and the type II pneumococcus is apparently based on S-anti-S reactions. It represents an example of heterogenetic specificity which is of particular interest because of the wide genetic separation of the pathogenic schizomycete and the saprophytic ascomycete. Data on the individual irregularity in the yeast-agglutinating capacity of serum from nonimmunized or "normal" rabbits are presented as experimental facts.

## AUTHOR'S SUMMARY

ANAPHYLAXIS WITH THE TYPE-SPECIFIC CARBOHYDRATES OF PNEUMOCOCCUS  
OSWALD T. AVERY and WILLIAM S. TILLET, *J. Exper. Med.* **49** 251, 1929

The type-specific carbohydrates (haptens) of pneumococcus types I, II and III, when isolated in protein-free form, are devoid of the property of inducing active anaphylactic sensitization in guinea-pigs. The bacterial carbohydrates of pneumococcus, of which the type II and type III substances are nitrogen-free, produce rapid and fatal anaphylactic shock in guinea-pigs passively sensitized with the precipitating serum of rabbits immunized with pneumococci of the homologous type, the reactions induced are type specific. In contrast to the positive results with immune rabbit serum, there is a complete absence of anaphylactic response to pneumococcus carbohydrate in guinea-pigs passively sensitized with antipneumococcus horse serum.

## AUTHOR'S SUMMARY

CELL ANTIGENS AND INDIVIDUAL SPECIFICITY. KARL LANDSTEINER, *J. Immunol.* **15** 589, 1928

Since species are characterized not only by morphologic attributes but by their specific biochemical constitution as well, it seems evident that the somatic and functional development of the organic world was paralleled by a biochemical evolution of the proteins and haptens. One must assume that the two lines of events are linked in some way, although no explanation has been offered as to how such a correlation might be brought about. In this regard it is essential to know whether the small initial steps in evolution are coupled with changes in the proteins. If so, individual and racial protein differences, perhaps too small to be detected by the methods available, ought to be a matter of regular occurrence. In the opposite cases it is conceivable that the transformation of proteins came about discontinuously, contingent on the occurrence of numerous changes or modifications of a special kind in the germinal constitution, perhaps in connection with hapten variations. It is too hazardous, attractive as it would be, to speculate further along these lines. Yet to perceive the problem may not be superfluous and may lead to experimental investigation.

## AUTHOR'S SUMMARY

PREVENTIVE VACCINATION OF THE NEW-BORN AGAINST TUBERCULOSIS BY  
B. C. G. A. CALMETTE, *Brit. J. Tuberc.* **22** 161, 1928

Calmette presents a brief argument and reasons for favoring vaccination of the new-born with B. C. G., and considers Great Britain one of the rare countries in which preventive vaccination does not yet seem to interest public health authorities. From July 1, 1924, to July 1, 1928, 96,000 children have been vaccinated in France with B. C. G., and the method has rapidly spread in many foreign countries, including Belgium, Holland, Norway, Sweden, Poland, Roumania, Russia, Bulgaria, Jugo-Slavia, Greece, Italy and Spain. In French Indo-China, 45,000 children have been vaccinated. Calmette submits himself and his claims to the judgment of the commission set up by the Section of Hygiene of the League of Nations. B. C. G. can be used on the new-born without the slightest fear of producing harm.

## H. J. CORPER

ALLERGY FROM DIPHTHERIA ANATOXIN. A. COMPTON, *Brit. M. J.* **2** 1175, 1928

On the third day after the third injection of anatoxin the patient developed a widespread urticaria.

BLOOD GROUPS AND DISEASES OF THE POPULATION OF SCHLESWIG-HOLSTEIN  
M GUNDEL, *Ztschr f Immunitätsforsch u exper Therap* **56** 60, 1928

The blood groups of 2,448 psychopathic patients were determined. A considerable increase of the frequency of group B was noticed among patients with dementia praecox, psychopathia and metasyphilitic diseases, while this group was present in normal or subnormal values among patients with epilepsy, and senile and arteriosclerotic dementia. A definite explanation of the causes could not be offered. The minor increase of group AB and the more marked one of group B among tabetic and parietic patients may be due to the fact that syphilitic patients of groups AB and B have a positive Wassermann reaction, which in most of the cases persists in spite of all efforts to make it negative. Group B was present in 9.3 per cent of the insane persons with blue eyes and blond hair, while it was found in 20.8 per cent of those with gray eyes and brunette hair and in 26.8 per cent in those with brown eyes and brunette hair.

W C HUEPER

SPECIFIC AND SUBSPECIFIC ANTIBODIES. W MARKOFF, *Ztschr f Immunitätsforsch u exper Therap* **56** 95, 1928

Antibodies of different character are produced if unchanged bacteria or bacteria more or less decomposed by bacteriophagic or fermentative action are introduced into the organism. Markoff differentiates between three types of antibodies. Antibodies of first degree are produced by the injection of unchanged bacteria. They possess a haptophoric group and are specific in action on the corresponding antigen. Complement-fixating substances, specific agglutinins, precipitins, etc., belong to this group. Antibodies of second and third degree are called subspecific antibodies. Antibodies of second degree resemble those substances effective in the protein therapy and follow the introduction of partly destroyed bacterial proteins. Partial agglutinins belong to this group. Antibodies of third degree result from the introduction of still more decomposed bacterial proteins. They react with group heterogenous proteins. The normal agglutinins and precipitins belong probably in this group. They are similar to the substances obtained in the nonspecific protoplasma activation after Weichardt.

W C HUEPER

EXPERIMENTAL INVESTIGATIONS INTO THE GROUP SPECIFIC ANTIGENS AND ANTIBODIES. GREGOR GREENFIELD, *Ztschr f Immunitätsforsch u exper Therap* **56** 107, 1928

Erythrocytes of group A gave a group specific complement-fixation test with some human serums. Alcoholic extracts gave even stronger reactions. The specificity could also be demonstrated by absorption tests. A group specific reaction was also obtained with saliva as antigen. Group specific precipitin reactions with alcoholic extracts could not be shown. The serum of rabbits injected with erythrocytes of group A contained species specific and group specific antibodies. Normal cattle serums treated with human erythrocytes of group AB agglutinated in twenty-three of fifty-four cases still erythrocytes of group O. The reaction was more marked at room temperature than at 2 C. Erythrocytes of group A and B showed occasionally also a weak agglutination. The anti-O-agglutinin could be separated again after its fixation on erythrocytes of groups O, A and B. Hearts of group O bound more strongly the anti-O-agglutinin than hearts of group AB. Hearts of group A took an intermediary position.

W C HUEPER

THE HETEROGENOUS SYSTEM IN HUMAN ERYTHROCYTES AND THE HETEROGENOUS HUMAN ANTIGEN IN ERYTHROCYTES OF ANIMALS. I L KRITSCHESKI and R E MESSIK, *Ztschr f Immunitätsforsch u exper Therap* **56** 130, 1928

The Forssman's antigen (sheep antigen) is present in erythrocytes of all men, independently from their blood groups. The human erythrocytes contain more-

over the antigens of Kritzschewski (chicken), of Friede (turtle), of Friede and Gruenbaum (cat) and that of Landsteiner-van der Scheer-Witebsky (hog) The heterogenous human antigen and that of hog is present in erythrocytes of sheep, chicken, turtle and cat

W C HUEPER

THE SIGNIFICANCE OF LIPOIDS IN IMMUNIZATION Ztschr f Immunitatsforsch u exper Therap **56** 191, 1928

The lipoids of normal serum, as well as those extracted from the liver and purified possess identical qualities and act in the same manner on bacterial and snake poisons and bacteria by binding and detoxicating the former, and by decreasing the toxicity of the latter The production of lipoids by the liver demonstrates the importance of this organ in the defense of the organism against intoxications and infections The lipoids act on the toxins in twofold manner They fix these substances and detoxicate them, producing atoxic products with immunizing properties The modifying effect of the lipoids on the toxins is considered by the authors as an important factor for the production of vaccination substances of toxic character as that is demonstrated by the modification of the toxicity of anthrax bacilli

W C HUEPER

### Tumors

THE CATALASE OF MALIGNANT TISSUE M R LEWIS and H COSSMAN, Am J Physiol **87** 584, 1929

It was found that extracts of inoculable chicken sarcoma of the Rous type were weak in catalase, in this respect resembling the muscle which the tumor invades They also depressed, although they did not prevent, catalytic activity of extracts of other organs Inactivation of the virus was affected by small amounts of peroxide, but the effect of this on the living tumor could not be determined, owing to the fact that the peroxide was promptly absorbed by the blood stream, with the production of fatal oxygen emboli Rat sarcoma and carcinoma were more active in respect to catalase than was the chicken tumor

H E EGGERS

THE RELATION OF HEREDITY TO CANCER MAUD SLYE, J Cancer Research **12** 83, 1928

The article is a polemic discussion with C C Little It brings out in great detail the ideas of Slye concerning the relationship between carcinoma and heredity

B M FRIED

MALIGNANT LYMPHOBLASTOMA J S MCCARTNEY, JR, J Cancer Research **12** 195, 1928

A case of malignant lymphoblastoma is described in which the organs showed a variable histologic structure corresponding in different areas to Hodgkins' disease, aleukemia, lymphoblastoma and endothelioma Another case of a pure endothelioma of the lymph nodes is given in detail

B M FRIED

THE NONGENETIC APPEARANCE OF VARIOUS TYPES OF NEOPLASIA IN EXPERIMENTAL ANIMALS? L C STRONG, J Cancer Research **12** 208, 1928

Strong affirms that the teachings that all types of neoplasia occurring in laboratory mice are brought about by the activity or functioning of a single mendelian determinant are not convincing The data of Maud Slye are believed by him to be neither consistent within themselves, nor with the more convincing data that have been accumulated by geneticists throughout the world in the last years He believes that the process of heredity is merely a means to an end and by its investigation one is able to throw some light on the neoplastic changes

that lead to the occurrence of neoplasia, then one may still believe that the science of genetics may throw some light on this phenomenon. His argument is substantiated by a report of a study of three types of tumors derived from the connective tissue element of the embryo

B M FRIED

THE INFLUENCE OF THE ALIMENTARY REGIMEN ON TAR CANCER J MAISIN and A FRANÇOIS, *Ann de med* **24** 455, 1928

The authors affirm that diet has an influence on the development and the growth of a tar carcinoma. A liver diet accelerates the rate of growth of a tumor making it malignant. The active substance present in the liver resists desiccation and remains potent in a dry state for several months. The nature of this substance is unknown to them.

B M FRIED

MULTIPLE CARCINOMAS M GOIDZIEHER, *Virchows Arch f path Anat* **267** 326, 1928

A case is described in which three independent carcinomas were present: a squamous cell carcinoma of the esophagus with metastases of the lymph node, a typical liver cell carcinoma with rupture into the portal vein, and a tubular adenocarcinoma in the liver, of cholangiocellular type. The origin of the last mentioned tumor is discussed, and is attributed to proliferated liver cells which have given rise to pseudobile ducts.

B R LOVETT

GENERALIZED LYMPHATIC VESSEL CARCINOMATOSIS WITH CHYLOUS ASCITES K SCHMUCKER, *Virchows Arch f path Anat* **267** 339, 1928

The author describes a carcinoma of the stomach, with extension into the lymphatics of the mesentery and abdominal organs, and farther into those of the entire body, especially of the skin. This extension could be explained by proliferation of the tumor cells in the lymph channels, with little tendency to tissue destruction. There was an extensive chylous ascites, due to diapedesis of chyle through the uninjured vessel walls. The milky character of the pleural exudate and the skin edema was caused by passage through the vessel walls of emulsified products of degeneration, arising from fatty changes and necrosis in the carcinoma cells.

B R LOVETT

A CARCINOMA IN A THREE YEAR OLD CHILD P ROSTOCK, *Virchows Arch f path Anat* **267** 352, 1928

A tumor of the sacrum, removed from a child, aged 3, proved to be an adenocarcinoma. This was not a carcinoma of the rectum in the ordinary sense, but may have originated from remains of the embryonic caudal gut.

B R LOVETT

AN UNUSUAL TUMOR OF THE PANCREAS A PRIESEL, *Virchows Arch f path Anat* **267** 354, 1928

An egg-sized, encapsulated tumor was found in the caudal end of the pancreas in a woman, aged 29. This was a solid epithelial growth, composed of large, finely granulated cells, and of at least limited malignancy, shown by the tendency of the cells to grow into the capsule and the presence of many mitotic figures. The origin of the growth was doubtful, probably either from the pancreas itself, or from misplaced rests of suprarenal cortex or liver. The cells bore the greatest resemblance to those of the liver.

B R LOVETT

MALIGNANT SACROCOCCYGEAL CHORDOMA J PODLAHA and F PAVLICA, *Virchows Arch f path Anat* **267** 363, 1928

Including the tumor here described, forty-four instances of sacrococcygeal chordoma have been reported in the literature. The tumor consists typically of



a mass of fibrous stroma surrounding the parenchyma, in which the characteristic cells and a basophilic exoplasm are found. The cells lie singly, in masses or in alveoli, with intercellular substance between the groups, resembling a carcinoma more than a sarcoma. Vesicular cells are found, containing either a single large vesicle or many small vacuoles. A second type of cell is the small angular cell, with eosinophilic protoplasm. Cysts are also seen within the tumor, surrounded by the mucous-like exoplasm, and apparently arising from destruction of the cells. The mass is rich in glycogen and fat. The malignancy of this tumor consists in its tendency to recur after removal, the growth is slow and metastases rare.

B R LOVETT

### Medicolegal Pathology

EMBOLISM AND THROMBOSIS OF THE ABDOMINAL AORTA M M BANOWITCH and G H IRA, *M Clin N Amer* **11** 973, 1928

In five patients, all women, the symptoms were very similar: an acute onset with shock and severe pain, tenderness, loss of sensation and paralysis of the lower extremities which subsequently became cyanotic and gangrenous. One woman had a decompensated heart resulting from arteriosclerosis and hypertension. In the other four there was mitral stenosis. Postmortem examinations of the bodies of two of the four were the only ones secured. The clots found at the bifurcation of the aorta were regarded as emboli from the heart with subsequent thrombosis into the femoral and other arteries.

Because the symptoms were so much alike the authors believe that riding emboli from the heart lodged at the distal end of the aorta in all of the five women and occluded one or both common iliac arteries. In three, embolism of other vessels preceded that of the aorta. A most important symptom is loss of pulsation in the arteries of the lower extremities. About 105 cases of obstruction of the aorta by thrombi or emboli, chiefly the latter, have been reported and during recent years the clots have been surgically removed a few times with complete recovery.

E R LE COUNT

TOXIC HEPATITIS AND HEPATOLYSIS FOLLOWING THE USE OF ATOPHAN M A RABINOWITZ, *M Clin N Amer* **11** 1025, 1928

Three more cases of poisoning from cinchophen, all followed by recovery, are added to the three deaths and nine recoveries already reported, making fifteen cases altogether. Apparently the toxicity of the drug is due to the benzene rings it possesses. The symptoms are those of acute yellow atrophy. The liver of a woman who had taken  $7\frac{1}{2}$  grams (0.49 Gm) three times a day for five months was greatly shrunken and practically without normal liver tissue. Rabinowitz also mentions five poisonings with two deaths from an iodine derivative of cinchophen (diiodatophan) which has been used for cholecystography. Cinchophen is especially dangerous when given to alcoholic persons, pregnant women, persons suffering from malnutrition or from other diseases associated with damage of, or a lessened amount of glycogen in, the liver.

E R LE COUNT

ERGOT POISONING AMONG RYE BREAD USERS I ROBERTSON and H T ASHBY, *Brit M J* **1** 302, 1928

GANGRENE FOLLOWING THE USE OF ERCOTIZED RYE BREAD W J DILLING and R E KELLY, *Brit M J* **1** 540, 1928

Among the Polish and German Jews in Manchester many poisonings from ergot were observed. They were found exclusively among those who ate bread made from rye harvested in the autumn of 1927, and grown during a cold damp season. The ergot was found identified by its physiologic reactions and the fungus was cultivated from the grain. Formication was an important symptom. One man

had gangrene of both hands. These observations from Manchester evidently stimulated the publication of the report by Dilling and Kelly which they made in Liverpool in 1923. This concerned symmetrical gangrene of the second toes requiring amputation of one in November, 1921, and of the other a year later. Ergot is most potent in flour made soon after harvesting and loses its strength as the grain dries. The patient was a Polish Jew, a salesman, aged 35, the ergot was found in the rye he ate. These writers emphasize the need of care in excluding Raynaud's disease and the obliterating thrombo-angitis which occurs almost exclusively in Jews.

E R LE COUNT

ACUTE SUPPURATIVE LEPTOMENINGITIS DUE TO TRAUMA WITHOUT DEMONSTRABLE WOUNDS. E EHNRROOTH, *Deutsche Ztschr f d ges gerichtl Med* **12** 30, 1928

There is but little adverse opinion to the important role trauma may play in causing the development of active syphilis or tuberculosis of the brain or of some tumors of the brain. With regard to the first two, it is believed that infection of the site injured occurs due to organisms in the blood stream. The injury of the head by direct or transmitted violence may be unaccompanied by any external wound, or the wound present may be insignificant. But there is little in the medical literature regarding a causal relationship between external violence which leaves no trace and infection of the brain or leptomeninges with ordinary pyogenic bacteria. A few cases have been reported in which it is claimed the bacteria gained entrance to the cranial cavity through existing fissures or crevices, or by lymph channels, and had their passage aided by trauma which left no wound or other injury. It is highly essential that symptoms should appear promptly after the injury to assume that violence has any part in causing the disease.

Ehnrrooth reports a meningitis which developed at once after a fall. The soldier, aged 20, struck his head when he fell, he was unconscious and headaches began that night. Death occurred two days later, and the meningitis was pneumococcal. The route of infection, presumably from some of the accessory nasal sinuses, was not ascertained at the postmortem examination. By putting virulent streptococci, staphylococci or pneumococci into the saphenous or ear veins of rabbits at the time when the animals were also hit on the head, the author found infection of the brain or its meninges in 68 of 152 animals used. He is not disposed, however, to apply these results in rabbits rigorously to similar occurrences in human beings.

E R LE COUNT

MURDER BY REMOVAL OF THE BOWEL. L HIRSCH and M KRESIMENT, *Deutsche Ztschr f d ges gerichtl Med* **12** 87, 1928

Almost the entire bowel together with the sac of a large umbilical hernia mistaken for a tumor have been amputated from a newly born infant. Large portions of the small bowel prolapsing through wounds of the uterus or vaginal fornix have been removed by abortionists. Insane persons (Loessel and Jakl *Deutsche Ztschr f d ges gerichtl Med* **8** 419, 1926) have stripped the lining of the colon away from the rest of the bowel, pulling it out through the rectum, this has also been done by persons not insane (Schackwitz *Deutsche Ztschr f d ges gerichtl Med* **10** 31, 1927). Apparently removal of the colon lining in this manner is easily accomplished and causes little pain or none at all.

Hirsch and Kresiment report the murder of a girl, aged 11, by her insane mother. The child was first hit on the head and then, with her hands alone, the mother tore out the perineum, the adjacent walls of the vagina and rectum, the uterus and its adnexa, the distal half of the colon and all of the small bowel except the duodenum. The child was illegitimate. The report is devoted chiefly to the insanity of the mother.

E R LE COUNT

## Technical

BRILLIANT-GREEN ENRICHMENT METHODS IN THE EXAMINATION OF FECES FOR ORGANISMS OF THE ENTERIC GROUP RUTH GILBERT and MARION COLEMAN, *J Infect Dis* **44** 21, 1929

This study would indicate that, for specimens which may be in transit twenty-four hours or more during submission to a laboratory, presentation in 30 per cent glycerol solution followed on receipt by inoculation of six plates of differential mediums would be a slightly better procedure for the isolation of *B typhosus* than the Havens method. The preparation of the brilliant-green bile solution requires careful standardization, and irregularities may follow its use if its preparation is not adequately supervised. The use of either the Rakieten and Rettger or the Havens enrichment method in addition to the routine procedure of the New York State Laboratories would furnish a slightly higher percentage of successful isolations. Regardless of the method used, the submission of a series of specimens from each individual would seem to provide the best opportunity for the detection of typhoid carriers.

## AUTHORS' SUMMARY

THE PRESERVATION OF BLOOD FOR SUGAR ESTIMATIONS H. LAX and I. SZIRMAT, *Munchen med Wchnschr* **76** 58, 1929

The glycolysis and bacterial destruction of the sugar in diabetic and normal blood are prevented by the addition of 1 per cent sodium fluoride and 0.1 per cent mercuric chloride. With the addition of these reagents the sugar content of the blood remained unchanged even after thirty days' storage in the incubator.

## AUTHORS' SUMMARY

SIMPLIFIED METHOD FOR BACTERIAL INDOL N. A. KOVACS, *Ztschr f Immun-tatsforsch u exper Therap* **55** 311, 1928

P-dimethylamidobenzaldehyde (Merck), 5 Gm, is dissolved in pure amyl alcohol, 75 cc, and concentrated hydrochloric acid, 25 cc, from 25 to 30 drops of this solution are added to broth cultures of bacteria. After a gentle shaking a violet-red color appears if indol is present in the broth.

## W. C. HUEPER

STAINING SPIROCHAETA PALLIDA IN FROZEN SECTIONS OF CENTRAL NERVOUS SYSTEM R. KANZLER, *Ztschr f d ges Neurol u Psychiat* **117** 171, 1928

Kanzler has modified the method of Jahnke as follows. The section is immersed for thirty minutes in a solution of ammonium bromide and formaldehyde. It is then washed and put in pyridine for fifteen minutes, washed again and immersed for ten minutes in a 0.5 per cent uranin solution. After being washed again, the sections are immersed for one hour in a 1.5 per cent silver nitrate solution at from 37 to 40 C, quickly heated in the silver solution over the flame, washed in distilled water, dipped and moved about for from two to four seconds in a solution of silver nitrate, soda and ammonia. Then, without being washed, they are placed for from three to five seconds in a 5 per cent formaldehyde solution. As soon as they have taken on a yellow or yellowish-brown color, they are placed in distilled water, which is changed several times, and consecutively in alcohol, beechwood creosote-phenol-xylene, and Canada balsam. The spirochetes are stained black, whereas the nervous tissue remains unstained.

# Society Transactions

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## NEW YORK PATHOLOGICAL SOCIETY

*Anniversary Meeting, Jan 10, 1929*

HARRISON MARTLAND, M D, *in the Chair*

### ENDOCARDITIS IN MALTA FEVER (UNDULANT FEVER) C E DE LA CHAPELLE

An Italian laborer, aged 38, was admitted to Bellevue Hospital, third medical division, complaining of fever. His past history revealed the important information that, while in Italy nine months previous to admission to the hospital, he drank goat's milk. He arrived in the United States one month later and was admitted to a hospital where a diagnosis of typhoid fever was made. After five months in the same hospital, he left and went to the country where he felt well for about three weeks. Attacks of chills, fever and headache, followed by pains throughout the body, began about that time. Several weeks before admission to Bellevue Hospital the small toe of the right foot became extremely painful and began to turn black.

On physical examination he presented dyspnea and a café au lait color of the skin. The small toe of the right foot was red, with some black discoloration, it was swollen and was extremely tender to touch. Petechiae were also present on the fourth toe. Both feet were edematous. The fingers presented definite clubbing. The heart was slightly enlarged, the first sound at the apex was of poor quality. A distant, musical systolic murmur was heard at the apex and transmitted to the left, another soft systolic murmur was elicited at the aortic area. The rhythm was regular, the rate, 96. The temperature was 101 F. The systolic blood pressure was 90, the diastolic, 60. Both the spleen and the liver were palpable and tender.

Several days later an Osler's node was observed on the tip of the fourth finger of the right hand. Three weeks later the patient complained of pain in the right thigh. The femoral pulse was scarcely palpable in this leg. Shortly before death some few days later, he complained of severe pain in the lower part of the abdomen and both groins.

The clinical diagnosis was (1) heart disease, (a) bacterial infection, active, (b) endocarditis, subacute, (c) regular sinus rhythm, (d) class 3, and (2) Malta fever.

Urinalysis revealed a trace of albumin, hyaline and granular casts, and an occasional white blood cell but no red blood cells. On admission, the patient had 3,930,000 red cells, with 48 per cent hemoglobin and 3,350 white blood cells with 69 per cent polymorphonuclears and 26 per cent lymphocytes. Just before death, the red cells numbered 2,600,000 with 60 per cent hemoglobin, and the white cells 2,200. The Wassermann reaction was negative.

Blood cultures taken on two separate occasions revealed a small, gram-negative, nonmotile organism, so small that its outline could not be clearly defined. These cultures, together with serum taken during life, were studied by Dr Charles Carpenter of the Diagnostic Laboratory of the New York State Veterinary College and reported by him as being a true type of *Brucella melitensis* A.

At necropsy the outstanding observations were as follows: massive vegetative and ulcerative endocarditis of the aortic valve, massive septic splenomegaly with multiple anemic infarcts, hemorrhagic glomerular and tubular nephritis, parenchymatous degeneration of the liver, massive subperitoneal hemorrhage in the right half of the abdomen, of unknown origin, and subungual petechial hemorrhages.

The heart appeared to be about normal in size and weighed 345 Gm. The two anterior aortic cusps were practically completely destroyed and replaced by a soli-

tary, creamish-white, granular mass of fused vegetations, irregularly round, rather soft and friable and approximating the size of a thumb. The posterior aortic cusp was distinctly thickened, and on its ventricular aspect, at about its center, presented a vegetation, the size of a pea, which was loosely attached and fell away apparently of its own weight. The muscle of the heart was pinkish and opaque, but was otherwise well preserved. The aorta was excellently preserved.

The patient undoubtedly became infected in Italy by drinking goat's milk shortly before coming to this country. The onset of the symptoms occurred about one month after his arrival here, at which time he was admitted to a hospital where a diagnosis of typhoid fever was made. The duration of the malady, therefore, was about nine months, simulating the subacute course of *Streptococcus viridans* endocarditis. The clubbing of the fingers, the enlarged spleen, the café au lait color of the skin and the embolic manifestations completed the picture of subacute bacterial endocarditis.

## DISCUSSION

HARRISON S. MARTLAND. I suppose that without complete bacteriologic identification this case might easily pass as an influenzal endocarditis. I believe that in about 5 per cent of Dr. Libman's original series of subacute bacterial endocarditis the condition was attributed to *B. influenzae*.

WARD J. MACNEAL. I should like to call attention to the rather difficult bacteriology of infections of this type. The prevalence of contagious abortion in dairy cattle is not well recognized and not sufficiently well known to the various workers in animal husbandry. Previous to 1909, I believe that all authorities on dairy husbandry doubted the existence of contagious abortion in cattle in the United States. In 1910, one of my assistants and myself isolated *Brucella abortus* of Bang from an aborting cow at the Illinois Agricultural Experiment Station (MacNeal, W. J., and Kerr, J. E. *Bacillus abortus* of Bang, the Cause of Contagious Abortion in Cattle, *J. Infect. Dis.* **7**: 469, 1910). This observation was reported at the subsequent meeting of the Society of American Bacteriologists at Ithaca, New York. The bacteriologists and veterinary pathologists present at this meeting were wholly unfamiliar with this organism at that time. Since then it has been shown that this condition is widespread in dairy cattle in this country. Apparently, the variety of microbe which is present in cattle is somewhat less virulent for man than is the variety which is present in goats. The bacteriologic distinction is not easy, but there seems to be a difference in virulence. The recognition of human infection due to the cattle type is rather rare. I presume there are less than 100 cases in the literature. It would seem that we have here a good reason for the pasteurization of milk in general, especially because of the difficulty of recognizing the disease when it exists in the cattle. Sometimes in pure-bred herds of cattle, producing the highest grade of milk, contagious abortion will be unexpectedly discovered. It seems to me that we should be cautious about the possibility of this disease existing in cattle, especially in dairy herds, it is difficult to recognize.

## THE SIZE OF THE CONSOLIDATED LUNG IN LOBAR PNEUMONIA. P. N. CORYLLOS and GEORGE L. BIRNBAUM

Are the consolidated lobes in lobar pneumonia larger than the healthy ones? Affirmative answers have been given by Barth (*Dictionnaire des sciences médicales*, 1888, vol. 26, p. 227), Blake (quoted by Cecil *Text Book of Medicine*), Leslie (Leslie and Alexander *Pneumonia*, 1924, p. 47) and Aschoff (*Pathologic Anatomy*, 1923, vol. 2, p. 284) and in textbooks on medicine and pathology. MacCallum (*Text Book of Pathology*, 1928, p. 517) and Delafield and Prudden (*Text Book of Pathology*, 1928) are noncommittal on this phase of the subject.

We are of the opinion that the affected lobes are smaller than the sound ones, basing this contention on experimental and clinical evidence (Coryllos and Birnbaum *Arch. Surg.* **16**: 501 [Feb.] 1928, *ibid.* **18**: 190 [Jan.] 1928, *Bull. N. Y. Acad. Med.* **4**: 383, 1928). In making autopsies on pneumonic dogs we first clamped the trachea before opening the chest and found this to be so. The pneumonic lung was

smaller and bluish black and was sunken toward the posterior part of the chest cavity. The size of the healthy lung was not here due to an expansion of the thorax, for these animals died with the chest in a phase of extreme expiration. The state of expansion of the sound lung was therefore dependent on and proportional to the shrinkage of the pneumonic lung. If the tracheal clamp was then released, the healthy lung collapsed to a smaller size than the diseased one. (This experiment was repeated at the meeting of the New York Pathological Society, Academy of Medicine, Jan 10, 1929.) These observations were clinically verified at autopsy of a man, aged 60, who died on the sixth day of the disease with pneumonia of the entire right lung. With the trachea clamped the chest was opened, and the left (healthy) lung appeared larger than the right, this impression was confirmed by measuring the water displacements of the respective lungs. It is necessary to proceed rapidly and avoid manipulation of the healthy lung because air diffuses rapidly through its alveolar surface. Clamping the trachea maintains the true relative size of the respective lungs uninfluenced by the opening of the chest with the consequent disappearance of the intrapleural negative pressure.

That such observations are to be found at autopsy is not surprising when it is considered that in the dog experimentally produced lobar atelectasis and lobar pneumonia are indistinguishable from one another by roentgenogram or even by the gross appearance of the lungs. Moreover, injection studies (to be published) of the pulmonary circulation show that there is an initial shrinkage of the alveoli in both diseases and later a marked impairment of the capillary circulation.

Against the view that the pneumonic lung is larger than the affected one is the fact that the heart and mediastinum have never been reported shifted toward the sound side in an uncomplicated case. On the contrary, shifting of the heart and trachea toward the affected side with elevation of the homolateral diaphragm (cardinal sign of atelectasis) has been reported in cases of lobar pneumonia in children by Thoenes (*Monatschr f Kinderh* **22** 353, 1924), Wallgren (*Acta pediat* **3** 81, 1922), St Engel (*Handb d Kinderh* [Pfaundler and Schlossmann] **3** 636, 1924) and Griffith (*Am J M Sc* **174** 448, 1927). However, the dictum of absolute rest and immobility for the patient, so generally ascribed to, has left the medical profession in sore need of such further useful data as could come from early serial roentgenograms in adults. Moreover, one seldom obtains postmortem examinations at the beginning of the disease, and knowledge about the early pathologic process is therefore limited.

We have thus come to regard lobar pneumonia as essentially a pneumococcic lobar atelectasis. That is, whereas lobar atelectasis is considered dependent on occlusion of a lobar bronchus (and absorption of alveolar air) with a relatively sterile and nontoxic bronchial exudate, lobar pneumonia is considered as a lobar atelectasis occasioned by occlusion of lobar bronchus with a viscid fibrous exudate laden with pneumococci the toxins of which poison the patient. In the latter instance it should be remembered that the concomitant alveolar exudation in pneumonia prevents as great a shrinkage of the lung as occurs in simple lobar atelectasis, spontaneous or after operation. At autopsy, therefore, the relative difference in size of the pneumonic and the healthy lung need not be so striking, especially in a late stage of the disease when there is already considerable alveolar exudate.

#### DISCUSSION

GEORGE L. BIRNBAUM. I wonder whether it has occurred to many what the cause of the indentations of the ribs in the pneumonic lung may be other than enlargement. There is not much question that the indentations are there. It seems to me that they can be accounted for by the simple explanation of gravity. In this way these indentations would mean pressure and weight of the edematous lung against the thoracic cage, rather than enlargement of the affected lobe.

HARRISON S. MARTIND. The paper presented is important. It is indeed gratifying to encounter research in pathology along purely mechanical, physical or chemicophysical lines and free from weird immunologic theories. Dr Coryllos and Dr Birnbaum have undoubtedly proved that the pneumonic lung is smaller

than the uninvolved lung For some time I have even thought that resolution in lobar pneumonia was due almost entirely to mechanical factors, and had little to do with special immunologic phenomenon

## CHICAGO PATHOLOGICAL SOCIETY

*Regular Monthly Meeting, Jan 14, 1929*

ESMOND R. LONG, *President, in the Chair*

### EXPERIMENTAL STUDIES ON COLLAPSE OF THE LUNGS IN THE RABBIT ROBERT G. BLOCH

These experiments were undertaken to study first, the mechanical effects of pneumothorax on the chest of the rabbit, second, the influence of the pleura, and third, the respiratory changes Collapse of the lung was caused in seventy normal rabbits over periods varying from five minutes to eleven months

The mediastinal structure does not permit leakage of air from the air-filled pleural cavity into the opposite side, but the mediastinum is extremely labile, and complete collapse of the lung displaces it to an extent which is not observed in man The heart does not rest on the diaphragm, but is suspended in the center of the thorax with two mediastinal pillars connecting it with the diaphragm The pillars are under slight tension and are easily movable They include a cavity which is filled by an additional (fourth) lobe of the right lung The diaphragm is flabby and gives way to intrapleural pressure more easily than in man It is concluded that the anatomic conditions in the chests of rabbits and of human beings are too different to apply the results clinically

Pneumothorax was maintained in most of the rabbits with intrapleural pressure of about +1 cm. of water which corresponds to a collapse under fairly high positive pressure in man Atmospheric air was used for collapse It is absorbed rapidly The average rabbit's lung reexpands completely within twenty-four hours after complete collapse Refillings had to be done daily at first to maintain pneumothorax The intervals between fillings could be lengthened after about one month and were gradually increased to seven days, which was found to be the maximum time that the lung will stay collapsed A marked noninflammatory thickening of the visceral pleura occurs, increasing rapidly after collapse of one month's duration No pleural exudation was observed No formation of adhesions occurred after the lung was permitted to reexpand In every case, it was easy to recollapse The absorption of air is directly proportional to the thickness of the pleura, and vice versa, the thickening of the pleura is most marked where it is most exposed to contact with the inflated air

The experiments on the respiratory changes due to collapse of the lung were instigated by the recent practice of simultaneous bilateral pneumothorax The abdominal and thoracic respiration were recorded during the procedure of collapse and afterward up to twenty-two hours, simultaneously with the intrapleural pressure Even extreme collapse does not change the abdominal respiration materially, but increases the thoracic respiration to five or six times its normal volume The change in respiration is not a shock effect, but the actual response to air hunger It follows readily the repeated removal and reinflation of air The results suggest that careful study should be made of the respiratory response of patients when collapse of the lung occurs before simultaneous bilateral pneumothorax is clinically accepted

#### DISCUSSION

E. R. LONG Is the opening of the alveoli under the pleura due to absorption of air from the pleural space, or was the periphery of the lung incompletely collapsed?

R. G. BLOCH The peripheral portions of the lung were collapsed

# A MICROSCOPIC CARCINOMA OF THE TESTIS CONCEALED IN CHRONIC GRANULATION TISSUE PAUL J. BRESLICH

This tumor in the testis of a man, aged 24, was concealed in a mass of dense fibrous tissue in which, with the tumor cells, were regions of chronic granulation tissue closely resembling that stimulated by *B. tuberculosis*. In the center of certain of these masses were necrotic cells or cellular detritus and ingrown epithelium arranged in bands and cords like liver trabeculi with little stroma. The stimulus for this unusual growth of granulation tissue may have been the chronic irritation produced by substances derived from testis tissue destroyed by the invading tumor, or liberated by necrosis of the carcinoma cells. Substances likely to cause this reaction are the lipins, especially cholesterol. Acid-fast bacilli were not found in these tissues.

# EXPERIMENTAL STUDY OF SOME IMMUNE REACTIONS TO ASCARIS HAMILTON R. FISHBACK

Various extracts of dried ascaris powder were used directly and after incubation with immune rabbit serum. The hemolytic action of saline and iodized oil 40 per cent extracts against human red blood cells was completely neutralized by the immune serum. The stimulating action on a uterine strip from a sensitized guinea-pig and the reactive effect on the skin of a sensitive human subject of the saline extract of *Ascaris* were not lessened by the immune serum, while the same activities of the iodized oil extract were inhibited by the immune serum.

## DISCUSSION

B. L. RAPPAPORT. The relation of human ascaris to hog ascaris is an interesting problem. There is no morphologic difference. Serologic tests have failed to differentiate.

# STUDIES IN EXPERIMENTAL CALCIFICATION AARON LEARNER

M. B. Schmidt, in his discussion of pathologic calcifications, divides them into two main groups:

(1) Calcifications occurring where there have been local tissue disturbances without any change in the calcium metabolism, (2) calcifications occurring in healthy tissues as a result of changes in the calcium metabolism.

The important conditions in the process are (a) oversaturation of blood and tissue fluid with calcium, (b) inability on the part of the excretory organs to excrete calcium satisfactorily, and (c) changes in solubility relations in the blood for calcium.

From the literature the following statements illustrate one or the other or several of these conditions:

Hofmeister stated that a decrease in carbon dioxide will lead to the precipitation of calcium when calcium supersaturation exists because of carbon dioxide increase. Such fluctuations by alternately varying the reaction, at the intervals of two days with diets the ash of which was respectively acid and alkaline, led to metastatic calcification in experiments by Rable and Dreyfuss. Calcium was deposited in practically all of the tissues of the white mice.

Katase, on the other hand, succeeded in obtaining metastatic calcification in guinea-pigs and rabbits by simple injection of various calcium salts. Calcium was deposited in all the tissues, but of especial interest is his description of calcium in the bronchial mucosa, and in the elastica, and he suggested that calcium is excreted in part through the bronchial mucosa. The two conditions that he considered important are oversaturation with calcium and also interference to some extent with the excretion of calcium.

Parathyroid extract-Collip is an agent capable of mobilizing calcium. Given in large dosage it produces hypercalcemia, 100 per cent or more, with attendant symptoms such as anorexia, emesis, somnolence, circulatory weakness and death.



Two questions arise What is the source of the calcium, and what are the pathologic consequences?

Stewart and Percival concluded, as had Greenwald and Gross, that the calcium enters the blood from the soft tissues or the bones, or both The bones, however, are the most likely source of the calcium, and they may well be considered as a reservoir for calcium much as the subcutaneous tissues are considered reservoirs for fat which is released when needed

To answer the question as to the pathologic consequences of an overdosage of parathyroid extract-Collip, the following experiments are presented

Several dogs were given injections of from 100 to 150 units of this drug The calcium value rose to 19.57 mg per hundred cubic centimeters of blood The dogs died with the symptoms mentioned Microscopically, there was only a marked decrease in the coagulation time of the blood, a hypertonic state and hyperemia of the gastro-intestinal tract Microscopically, calcium as demonstrated by Kossa's silver nitrate reaction, was found practically in all the organs and tissues of the body

Especially interesting were those livers in which calcium was found in the liver cells and also in the Kupffer cells In the lung, the calcium was in the elastica tissue of the alveoli and in the tunica propria of the bronchi The epithelium was desquamated because of the large amount of calcium In the kidney the calcium was present chiefly in the lumina of the tubules, in Bowman's space, and less so in the vessels and connective tissue

From the standpoint of the conditions involved, the following facts apply In the lung, stomach and heart, there was increased alkalinity consequent to the acids formed, and in the liver there was supersaturation, a factor also effective in all tissues Inability of the excretory organs to cope satisfactorily with the excretion of calcium was another factor

Of interest is the effect of the amount of calcium in the diet in the deposition of calcium in the tissues with and without associated injections of parathyroid extract-Collip

Fifty mice were divided into three groups (1) those fed a diet without calcium, (2) those on a diet with an amount of calcium equivalent to the salts of milk and (3) those on a diet containing twice the amount of calcium given in group two. Each group was divided into two parts, one part receiving injections, the other not Each mouse received 17 units in five weeks, then a number of mice at one dose received 10 units These are enormous doses Sussmann, in determining the calcium variation in white mice by the use of parathyroid extract-Collip stated that 10 units per mouse of 20 Gm is equivalent to giving to a man weighing 64 Kg a dose of 20,000 units He noted no clinical disturbances nor any rise in blood calcium These chemical determinations are in accord with our histologic observations Microscopically, no calcium was found in any of the organs except in the bronchial cartilages But caution is necessary in interpretation, for calcified bronchial cartilages are found in normal mice though possibly not with the frequency observed in the experiments

Interesting to note is the reported unresponsiveness of white mice and white rats to other hormonal substances, as reported by Voegtlin and Dyer in some experiments with epinephrine and pituitary extract

*Conclusions*—Mice are unresponsive to parathyroid extract-Collip

In dogs, large doses of this drug lead to death and to metastatic calcification of the gastro-intestinal tract, heart, lungs, liver, kidneys, pancreas, etc

The calcium in the lung and the arrangement in and under the bronchial mucosa gives morphologic support to Katase's suggestion that calcium is excreted in part through the bronchi

Furthermore, the presence of calcium in the glomerular tufts and Bowman's space and in the lumina of the tubules gives definite morphologic support regarding the excretion of calcium in the kidney, namely, through the glomerular tufts

## DISCUSSION

DELA HALPERT Was the calcium content of the bile determined?

AARON LEARNER No

R H JAFFE The studies are important in demonstrating that calcium is eliminated through the bronchi and in the glomerular tufts of the kidneys

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*Regular Meeting, Feb 11, 1929*

ESMOND R LONG, *President*, in the Chair

DEATH OF DR A A MAXIMOW R H JAFFE

Alexander Alexandrovitsch Maximow was born in St Petersburg, Russia, on Jan 22, 1874, the son of a well-to-do merchant. He attended the German high school there and entered the Imperial Military Academy of Medicine from which he graduated in 1899. After two years of postgraduate work in Germany, especially under Ernst Ziegler in Freiburg, he returned to his alma mater to engage in research work on the embryology of the blood and the histologic changes in inflamed connective tissue. His monograph on the inflammatory formation of connective tissue attracted much attention. At the age of 29 he became head of the department of histology and embryology at the university from which he had graduated. He held this position for nineteen years. In 1912, he received the degree of Doctor of Science from Trinity College, Ireland. The Russian revolution and the hectic years of the early Bolshevik regime interfered greatly with his work. As counselor to the Imperial Russian government and Physician General to the Imperial Russian army, he could not accustom himself to the development in his native country. When an opportunity was offered to come to the United States he gladly accepted. In the early spring of 1922, he escaped the spies surrounding him, made an adventurous flight over the Baltic Sea to Sweden from where he embarked for New York. In May, 1922, he was appointed professor of anatomy at the University of Chicago. It was in this position that he reached the peak of his productivity. In the midst of his work, engaged in numerous research problems he was called away. On the morning of Dec 3, 1928, the unexpected, terrible message came that he had died suddenly. Post-mortem examination revealed as the cause of his death a severe coronary sclerosis.

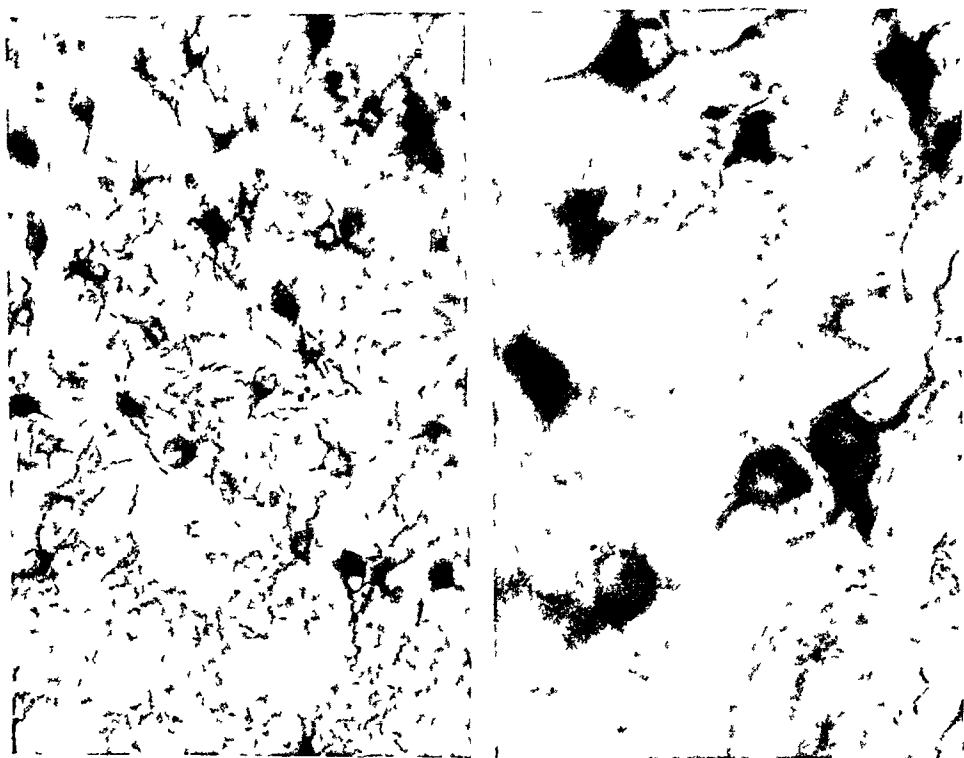
Maximow's life work was the study of the development of the blood cells, their relation to each other and to the cells of the connective tissue. Limited as the field appears at first glance, he made it a science in itself. Whenever new methods were discovered he applied them with rare technical skill in order to learn more about the resting wandering cells, lymphocytes and polyblasts. Vital staining and supravital staining and, during the last years especially, tissue cultures seemed to prove his conception which he had expressed already in his earliest publications and which he had fought for with great energy throughout his life, namely, that the small lymphocytes may become transformed into macrophages, monocytes and the other cells of the circulating blood. Time does not permit a list of all his contributions. Mention is made only of his recent studies: the formation of tubercles in tissue cultures, the behavior of the Calmette-Guerin tubercle bacillus in explanted tissue, the development of the reticular and collagenous fibers in tissue cultures, and the mesothelium.

In 1913-1914, Maximow published a textbook of histology in two volumes in Russian. The war prevented its translation and thus it did not become widely known. The lack of an adequate, modern and concise presentation of this subject in the English language induced Maximow to undertake the task of writing such a book. It was three-fourths completed at the time of his death. It is to be hoped, however, that the work will be completed as a monument to this great and genial man.

## OLIGODENDROGLIOMAS OF THE BRAIN PERCIVAL BAILEY and P. C. BUCY

In 1924, in examining the gliomas in the collection of Dr Harvey Cushing, one of us noted certain cellular tumors of slow growth whose nuclei resembled those of the oligodendroglia. The tumors contained a few neuroglial cells and much delicate intercellular material which could not be sharply stained or impregnated in any way. Although the tumors were believed to consist essentially of oligodendroglia and although they were called oligodendrogliomas (Bailey and Cushing, *Tumors of the Glioma Group*, 1926), positive proof could not be obtained because the pathologic specimens were not properly fixed to permit the use of Hortega's specific method.

Recently Globus (*Arch Neurol & Path* 19 263 [Aug.] 1927) and Penfield (*Am J Path* 4 153, 1928) have so modified the method of Hortega that it can be used on material fixed in 10 per cent neutral formalin. Working with this



Oligodendroglioma. Globus-Penfield modification of the silver carbonate method of del Rio-Hortega. At the left, numerous fairly normal oligodendroglia,  $\times 320$ . At the right, the same cells under a higher magnification,  $\times 780$ .

modified method we first proved, in October, 1928, that a tumor of the brain was actually composed of oligoglia. Since then we have identified twelve other similar tumors.

The accompanying illustration shows typical cells from an oligodendroglioma of the type described. At the left are seen numerous cells resembling normal oligoglia, to the right the same cells appear under a higher magnification.

## DISCUSSION

PETER BASOE. How are these cells differentiated from neuroglia, and do they occur in all parts of the brain?

P. BAILEY. There are certain distinct differences in structure between the oligodendroglia and glia cells. The staining procedure was carefully controlled by normal tissues. These cells occur in all parts of the brain and spinal cord.

wherever there are long medullated fibers. The tumors are rather avascular, tend to calcify, and are favorable for operation.

#### TRAUMATIC ANEURYSM OF THE AXILLARY ARTERY E. L. MILOSLAVICH

A man, aged 64, weighing about 230 pounds (104.3 Kg), fell on his left side and dislocated the left humerus (subcoracoid luxation), which was reduced without particular difficulties. An excruciating pain which appeared at the time of the dislocation persisted for several days. About four weeks after the accident, a tumor the size of an orange appeared in the left armpit and grew gradually until it reached the size of a large grapefruit. This growth was clinically interpreted as a sarcoma. The patient died about three years after the accident with symptoms of pulmonary involvement which were believed to be sarcoma metastases. At no time was there any noticeable pulsation of the tumor nor were there any signs of circulatory disturbances in the left arm.

The autopsy demonstrated an aneurysm of the left axillary artery, 18 by 17 by 12 cm. Both axillary arteries showed an advanced atheromatosis with intimal ulcerations. Identical changes, but to a more pronounced degree, were present in the inner lining of the entire aorta. The heart showed an eccentric hypertrophy of its left ventricle but no valvular lesions.

At the time of the dislocation, an injury occurred to the already diseased (atheromatous) axillary artery, leading to a rupture of its inner layers (incomplete or inner rupture of the artery). A complete laceration of the artery did not occur at the time of the accident or during the surgical reduction as no hematoma was observed. The aneurysm developed gradually until it reached the aforementioned unusual size. Similar observations were made by Stimson, Koerte, Kraemer, Hoffmann and others. Aneurysm of the axillary artery is an uncommon but characteristic complication of the dislocation of the humerus.

#### DISCUSSION

R. H. JAFFE. It would seem that with so large an axillary aneurysm there must be some unusual disease of the vessel wall such as an arteritis. What did the microscopic examination demonstrate?

E. L. MILOSLAVICH. The only changes observed microscopically were those characteristic of senile atheromatous sclerosis.

#### PRIMARY CARCINOMA OF THE DUODENUM H. D. COUNTRYMAN

Carcinoma of the duodenum, according to Lewis and Morse (*New England J Med* **198** 383, 1928), was first reported by Hamberger in 1746. His patient had a scirrhus carcinoma of the first portion of the duodenum which perforated the wall and caused peritonitis. According to the report of Eusterman, Berkman and Swan (*Ann Surg* **82** 153, 1925), carcinoma of the duodenum constitutes about 15 per cent of all intestinal carcinomas which, in turn, compose 10 per cent of all carcinomas. Brill (*Am J M Sc* **128** 824, 1904) computed from the combined statistics of Maydle, Nothnagel, Mueller and Lubarsch that 0.3 per cent of all intestinal carcinomas occurred in the duodenum. Deaver and Radwin (*Am J M Sc* **159** 267, 1920) stated that carcinoma of the duodenum was responsible for 0.033 per cent of all deaths. Statistics vary as to the frequency of carcinoma in the anatomic divisions of the duodenum. This is probably because carcinomas of the second or intermediate portion are confused with those of the ampulla of Vater. According to Deaver and Radwin, 22.15 per cent occur in the pars superior, 65.82 per cent in the pars intermedius and 12.02 per cent in the pars inferior. Statistics taken from elsewhere do not entirely agree with these. Eusterman, Berkman and Swan reported six in the pars superior, six in the pars intermedius and three in the pars inferior. Lewis and Morse reported twelve carcinomas of the duodenum: five in the first portion, five in the second, and two in the third. Figures as to their relative frequency in sex are not conclusive, but it is generally held that there have been a few more in men than in women.

Most of the carcinomas occurred in persons between the ages of 50 and 60 and the youngest age recorded was a 16 year old patient of Ewald Perry and Shaw (*Guys Hosp Rep* 50 214, 1893) observed one in a patient, aged 80 Etiologically, little more is known of duodenal carcinoma than of other forms The greatest contention is whether or not duodenal carcinomas arise from duodenal ulcers All of the views in regard to this subject are purely hypothetic, but it seems that duodenal ulcers have little etiologic importance Duodenal ulcers occur frequently, whereas carcinoma is rare, and the greatest proportion of duodenal carcinomas occur in the second portion of the duodenum where ulcers are seldom found

Grossly, carcinoma of the duodenum may be polypoid, infiltrative scirrhous which often is circular and narrows the lumen, or a soft, raised tissue Histologically, they usually have a tubular structure Next in frequency are those with an alveolar structure and an abundant fibrous stroma Only one colloid carcinoma of the duodenum has been reported (Letulle *Bull Soc anat de Paris* 11 721, 1897) The carcinoma which I report has a papillary structure

Duodenal carcinoma may arise from the epithelium of the Lieberkuhn crypts, Brunner's glands or pancreatic rests Orator (*Arch f klin Chn* 134 736, 1925) suggested that carcinomas of the pars superior may also arise from gastric mucosa which has extended into the duodenum In a previous article he stated that gastric mucosa often extends for a short distance into the duodenum He quoted Scagliosi who stated that many duodenal carcinomas result from a hyperplasia of Brunner's glands associated with ulcers

Carcinoma of the duodenum as a rule form metastases slowly In twelve reported by Lewis and Morse only three had spread widely, and two others had invaded the regional lymph gland The secondary growths, when present, usually are found in the regional lymph glands, the liver and the lungs

*Report of Case*—M H, aged 42, a salesman, entered the service of Dr H E Jones, St Luke's Hospital, on Aug 13, 1926, because of weakness and jaundice for two months and attacks of dizziness for three days He had measles at the age of 4 years and typhoid fever at 13 For a week he had had one or two tarry stools each day and had lost 50 pounds (22.7 Kg) He was markedly jaundiced but well nourished, suffered no pain and weighed 225 pounds (102 Kg) On the right side of the abdomen there was a palpable smooth mass which seemed to be connected with the liver but was not tender Roentgen examination disclosed a dense shadow extending below the right leaf of the diaphragm There were 1,945,000 erythrocytes, 17,250 leukocytes and 39 per cent hemoglobin The coagulation time was four hours and twenty minutes There was bile in the urine and occult blood in the stools Following two blood transfusions a cholecystectomy was performed on Dec 4, 1926 At the time of operation the gallbladder and common bile ducts were markedly dilated although a probe was passed readily into the duodenum Abnormalities of the duodenum or stomach were not detected by palpation The postoperative recovery was excellent The patient gradually regained 20 pounds (9 Kg) and his appetite returned The jaundice which had been decreasing even before the operation continued to diminish The patient was discharged and remained well until Dec 10, 1927 When examined by Dr Greer he was weak and anemic The skin was not appreciably jaundiced, but bile was found in the urine, and blood in the stools His condition progressively grew worse, and he lost considerable blood in the feces He died on May 12, 1928, soon after receiving 500 cc of blood and 500 cc of normal physiologic solution of sodium chloride intravenously

In the lining of the duodenum was an indurated cauliflower-like growth beginning 6 cm below the pyloric ring on the posterior and left sides of the wall The growth extended down the remainder of the pars intermedia and into the pars inferior for 3 cm, the entire length of the tumor being 12 cm At its widest portion about on a level with the papilla of Vater it was 3.75 cm wide, here it encircled one half of the circumference of the bowel The margins were raised and wavy and the tissue in the center was friable and grayish pink The papilla

of Vater was encroached on in the posterior edge of the growth. The common bile duct and pancreatic duct opened separately through small orifices into the lumen of the duodenum. At a level 2 cm below the papilla the lumen of the duodenum was one-half obstructed by the tumor, elsewhere it was from one-fourth to one-third obstructed. On surfaces made by a transverse section through the duodenum and adjacent head of the pancreas, at a level 2 cm below the papilla the muscularis beneath the tumor was thin, in places the growth had penetrated and had infiltrated slightly the surrounding pancreatic tissue for a distance of 1 cm. The descending portion of the duodenum above the tumor was distended slightly and pulled up by fibrous adhesions attached to the gallbladder fossa. The biliary lymph glands formed an indurated mass 6 by 5 by 3 cm. The lymph glands along the superior edge of the pancreas to within 6 cm of the tail were firm and as large as 1 cm in diameter. Continuous with the enlarged biliary lymph glands were enlarged firm lymph glands around the right renal vessels. There were two or three small shotlike lymph glands along the greater curvature of the stomach. All the surfaces made by cutting these glands contained many tumor nodules. The tumor surrounded the terminal 175 cm of the duodenal end of the common bile duct, proximal to this area the common bile duct was dilated so that at the level of the cystic duct it was 4.5 cm in circumference. The hepatic ducts were markedly dilated. The lining of the common and hepatic bile ducts was everywhere smooth even where the common duct opened through the papilla of Vater. The lining of the pancreatic duct was also smooth although the lumen was greatly dilated. The growth completely encircled the walls of both the common duct and pancreatic duct in their course through the papilla of Vater, but the linings here were unaltered.

The receptaculum chylum contained in its dilated lumen a pearly-white papillary mass of tissue 1 by 1 by 1 cm attached by a thin pedicle and resembling the egg masses of fish. There were also two constrictions in the thoracic duct completely encircling the wall and causing a puckering of the surrounding fat tissue. Each constriction was about 1 cm long, one was in the midthoracic portion, the other just above the receptaculum chylum.

The lower margin of the liver was at the costal edge on the right side and it weighed 2,120 Gm. Both its external surface and surfaces made by cutting were studded with many white, irregular nodules as large as 1 cm in diameter. The bile ducts were dilated. All the lobes of the lungs contained scattered tumor masses 1 to 2 mm in diameter. The wall of the left ventricle of the heart was hypertrophied. There was an acute hyperplasia of the spleen, and the small and large bowel contained tarry feces.

Histologically, in sections of the duodenum taken from the edge of the tumor there was a small piece of mucosa with normal villi and Lieberkuhn glands but with a stroma infiltrated by plasma cells and occasional tissue eosinophil leukocytes. Many of the epithelial cells contained large droplets of mucin. Rather abruptly at one place the mucosa changed into long slender papillae with fibrous stalks covered by large columnar cells with pale vesicular nuclei and acidophilic cytoplasm. From this place the mucous membrane was converted into a large mass of tissue projecting into the lumen, it consisted almost entirely of papillary structures with thin vascular fibrous stalks infiltrated in many places by aggregates of plasma cells, tissue eosinophil leukocytes, and in some places by polynuclear leukocytes. There were only occasional mitotic figures in the lining epithelial cells. Scattered irregularly in the stroma were small aggregates of cross-sections of acini resembling those of Lieberkuhn glands. These were lined with tall epithelial cells, a few with large droplets of mucin. In some places in longitudinal and cross-sections of Lieberkuhn glands there was a gradual transition from the normal epithelial cell of the mucosa to the larger columnar cell with a paler nucleus which is characteristic of the cells lining the papillary structures. The submucosa contained many mucous glands of Brunner and there were a few small aggregates of these in the tumor tissue. In some places the papillary masses of cells and a few large irregular acini of tumor cells extensively infiltrated the

muscle layer as well as the fibro-areolar tissue and adjacent pancreatic tissue. These tissues also were greatly infiltrated by lymphocytes. The tumor cells in the tissues such as the lymph glands surrounding the duodenum tended to occur in acini rather than as papillary structures.

In the periaortic, peripancreatic and right suprarenal lymph glands there were large nodules of tumor tissue with the same papillary structure as that of the growth in the duodenum. There were also acini formed by tumor cells, in the lumen of many of these were necrotic cells. The normal architecture of all of these glands was destroyed and there was only a small amount of unchanged lymphoid tissue.

The tumor mass in the receptaculum chyli, and the nodules of tumor tissue in the lungs and liver all had the same papillary arrangement as that found in the duodenal tumor.

In diagnosing this tumor as a primary carcinoma of the duodenum, tumors arising from the epithelium of the ampulla of Vater, the common bile duct, the pancreatic duct and the head of the pancreas were considered. As the tumor did not involve the pancreatic tissue extensively and the microscopic structure was unlike the customary tubular or alveolar arrangement of pancreatic carcinomas, this source could be excluded. Its diagnosis as a tumor of the ampulla of Vater or the adjacent common bile duct was opposed by the following features. The lining of the ampulla and common bile duct was everywhere smooth and covered with mucous membrane, the ampulla of Vater was on the edge of the tumor and not near the center as would be expected if it were the primary source. Carcinomas of the ampulla are usually small and confined to that region. These same statements apply in eliminating the pancreatic duct as a source.

#### PERFORATE POSTERIOR TRICUSPID LEAFLET (Double Tricuspid Orifice) J J LUTZ

Double auriculoventricular orifice is rather a rare condition, and double tricuspid orifice is extremely rare. A second valvular opening, however, supplied with its own cusps, chordae tendinae and papillary muscles may exist within the segments of an otherwise normal auriculoventricular valve. Maude Abbott has a collection of seven specimens, six of which are double mitral orifices, and only one double tricuspid (Osler *Modern Medicine*, vol 4, p 759, Greenfield *T<sub>1</sub> Path Soc London* 27 128, 1876, Cohn *Inaug Diss*, Königsburg, 1896, Degen *Inaug Diss*, Greifswald, 1903, Stuhlenweisenburg *Centralbl f allg Path, u path Anat* 23 342, 1912, Camisa *Centralbl f allg Path u path Anat* 23 1027, 1912, Pisenti *Di una rarissima anomalia della tricuspidalis*, Paraguae, 1888).

In addition to these seven, there is a specimen of double mitral orifice in the Harvard museum and one in the McGill museum, and another double tricuspid orifice reported by Gutzeit (*Arch f path Anat u allg Path* 241 355, 1923).

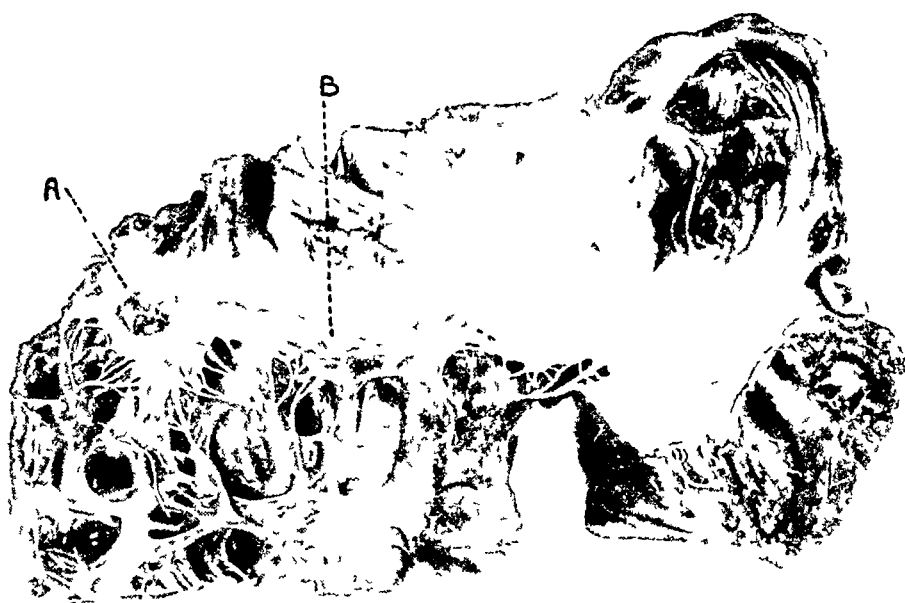
In Stuhlenweisenburg's specimen, and one of Camisa's, the two openings are of equal size and are separated by a bridge of valve tissue which furnishes a cusp to each of the orifices. In the others, the second opening is much smaller than the other and is contained within one of the leaflets. The specimen herein reported is of this type.

The double foramen usually causes no symptoms as it is a functioning valve. In four of the seven specimens reviewed by Abbott, the valves were thin, smooth and competent, while chronic endocarditis was present in the other three.

An unusual traumatic foramen in the anterior leaflet of the tricuspid valve is reported by Lauche (*Arch f path Anat u allg Path* 241 16, 1923). The patient, a man, aged 24, came to autopsy with a clinical diagnosis of cardiac failure with edema. On opening the right side of the heart, an oval foramen 0.8 cm in diameter was found in the anterior leaflet of the tricuspid valve. The edge of the foramen was uniformly thickened, yellowish white and somewhat retracted. Chordae tendinae of normal appearance ran from the lower edge of the opening to the papillary muscles. From gross observations an anatomic diag-

nosis of congenital foramen in the tricuspid valve was made, but microscopic examination revealed evidence of old inflammation and the presence of scar tissue. A careful inquiry into the past history of the patient disclosed that fifteen months previously he had received a stab wound in the second or third intercostal space. After apparent recovery he gradually developed symptoms of cardiac failure and died after a few weeks in the hospital.

The specimen described in this report is similar in size and shape to that reported by Lauche. A white man, aged 43, was first admitted to the hospital on Oct 13, 1926, complaining of attacks of dizziness, increasing weakness and jaundice of two months' duration. He was perfectly well previous to the onset of this illness. On examination, there was a generalized icteric tinge to the skin, and blood counts showed a severe anemia. There were 2,340,000 red cells, 11,600 white cells and the hemoglobin was 29 per cent. There was bile in the urine and blood in the stools. A transfusion of 400 cc of blood was given. Although the patient continued to bleed from the bowel, the blood constituents rose. On Dec 4, 1926, an exploratory operation was performed. A large distended gallbladder



Tricuspid ring laid open (natural size) *A*, opening in posterior leaflet, note chordae tendinae and tendency toward formation of leaflets, *B*, small foramen in septal leaflet

with multiple adhesions was removed. The patient improved rapidly after the operation, and left the hospital on Jan 21, 1927. The red cell count was then 4,430,000, the hemoglobin 49 per cent and the white cell count 11,950. There were no symptoms until December, 1927, when weakness and loss of weight reappeared. The patient reentered the hospital on Feb 12, 1928, with a pronounced secondary anemia, but no changes suggestive of pernicious anemia. Two blood transfusions were given, but the patient responded poorly. He left the hospital in April, very anemic, and returned a month later, on a stretcher, in a semicomatose state. He was again given a transfusion, but died shortly after the transfusion was completed. There were thus no symptoms to indicate any lesions of the valves of the heart.

The heart, with 2 cm of aorta attached, weighed 345 Gm on May 21, 1928. It was yellowish red, firm and greasy. The epicardium was yellowish pink, smooth and translucent. There was a layer of fat over the entire heart which was 8 mm thick over the right auricle, 3 mm over the right ventricle, 1 mm over the left



ventricle and 7 mm at the apex. The coronary arteries were buried in 4 mm of fat, and were straight and patent throughout. The lining was yellowish pink, studded with yellow, raised patches measuring 1 by 2 mm. These were most numerous in the proximal portions of the vessel. The apex was made up entirely of the left ventricle.

The lining of the right auricle was yellowish pink, smooth and glistening. The foramen ovale was closed. The opening of the coronary sinus was half covered by a thin, semilunar thebesian valve. The wall of the auricle was 2 mm thick at the base of the heart. The tricuspid ring, opened, measured 14 cm. The leaflets were thin, smooth and translucent. There was a foramen 10 mm in diameter in the posterior leaflet. A group of chordae tendinae extended from its edges to a small papillary muscle, forming the outline of a cone. In the septal leaflet there was an opening 2 mm in diameter. The lining of the right ventricle was yellowish pink, smooth and glistening. Shining through it, the myocardium was pale yellowish red, with lighter, more opaque yellow stripes. These changes were seen better in the left ventricle, but occurred most markedly in the papillary muscles of both ventricles. The surfaces made by cutting were pale yellowish red, and the opaque yellow streaks were best seen near the endocardial surface. The lining of the left auricle was similar to that of the right. The wall was 1.5 mm thick at the base of the heart. The mitral ring, laid open, was 11 cm, part of it has been cut away. The leaflets were yellowish pink, twice the normal thickness and roughened by fibrous tissue, covered with smooth endothelium, and by slightly raised, opaque yellow patches, some of which were 3 by 2 mm in diameter. The ventricular cavity measured 10 cm from apex to pulmonic ring. The pulmonic ring, opened, measured 10 cm. The leaflets were thin, smooth and translucent. As the heart had been opened previously the water test could not be applied. The lining of the left ventricle was similar to that of the right. The streaked appearance was more marked than in the right ventricle. The outer wall was 8 mm thick at the apex, 15 mm midway between apex and base of heart, and 20 mm at the base. The septal wall was 15 mm thick at the apex, 10 mm midway between apex and base, and 8 mm at the base. The ventricular cavity from apex to aortic ring measured 11 cm. The aortic ring, laid open, was 7.5 cm. Part of it had been cut away. The leaflets were thin, smooth and translucent. The lining of the aorta was yellowish pink, studded with slightly raised opaque yellow patches, some of which measured 4 by 5 mm.

In the section of papillary muscle stained with sudan III, 90 per cent of the section contained red-staining globules arranged in transverse and longitudinal bands. In the section through the outer wall of the left ventricle the same amount of red globules was present, but the arrangement in bands is not so marked. In the section of aorta, similarly stained, about 35 per cent of the intima contained red-staining globules.

The anatomic diagnosis was marked fatty changes of the myocardium, mitral leaflets, and lining of the aorta and coronary vessels, congenital foramina in the posterior and septal leaflets of the tricuspid valve, and slight hypertrophy of the left ventricle.

#### DISCUSSION

H. G. WELLS. A report of double mitral orifice was made to this Society several years ago. This anomaly was observed also in a dog at about the same time.

E. R. LECOUNT. The hole in the valve described was near the tricuspid ring and not at the margin as were the so-called fenestrations.

## Book Reviews

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CHRONIC (NONTUBERCULOUS) ARTHRITIS PATHOLOGY AND PRINCIPLES OF MODERN TREATMENT By A G TIMBRELL FISHER Price, \$8.75 Pp 232, with 186 illustrations contained in 93 plates (1 colored) London H K Lewis & Company, 1929

Monographs and papers on arthritis are appearing in ever greater frequency and are often of considerable importance. Fisher, an eminent British surgeon, has approached the problem in a thoroughly logical manner. His discussion of nomenclature leaves much to be desired, but when the classifications proposed are based on mixtures of pathology, etiology and clinical signs it seems impossible as yet to reach any satisfactory conclusions. The chapters on the physiology and pathology of the joints are admirably presented and especially well illustrated. The author bewails the fact that so little is known about the normal physiology of joints and suggests several lines of endeavor in this field. Using the most common English classification of rheumatoid arthritis and osteo-arthritis, Fisher describes the dominant pathologic manifestations of each, at the same time admitting that they may both come to the same end, though by different processes.

The etiology is somewhat briefly but well handled, although the role of traumatism in the causation of osteo-arthritis is perhaps overemphasized. When it comes to symptomatology the author makes an attempt to differentiate between the rheumatoid and osteo-arthritic types as clearly as he has pathologically. This differentiation is sometimes not difficult, but more often, at least in the advanced stages, the clinical picture may be so confusing as to make this impossible. Finally in the chapter on treatment Fisher discusses several lines of attack—medical, dietary and surgical. There is considerable space devoted to surgical treatment, and this portion bears the imprint of a capable and experienced surgeon.

On the whole this book is a splendid contribution to the subject, and is particularly stimulating in promoting further observations on the etiology, pathologic changes and normal physiology in their relationship to chronic articular processes.

MANSON'S TROPICAL DISEASES A MANUAL OF THE DISEASES OF WARM CLIMATES Edited by PHILIP H MANSON-BAHR, M D, Physician to the Hospital for Tropical Diseases, London Ed 9 Revised Price, \$11 Pp 921, with 35 plates, 401 figures in the text, 6 maps, and 34 charts New York William Wood & Company, 1929

The purpose of Patrick Manson in writing his book was to present in handy form essential information about the diseases of warm climates. The appearance at this time of the ninth edition, revised, shows that the book has proved to be of large practical service. The editor of this edition has done his part well. Much new knowledge has been incorporated and, when necessary, as in the case of yellow fever, previously accepted views and ideas have been abandoned. The general arrangement of the text is unaltered and the number of pages is about the same as in preceding editions. To quote from the preface: "Attention has been especially devoted to the subject of treatment—now, happily, becoming more and more stabilized—in recognition of the paramount position that clinical study and clinical methods still hold in Tropical Medicine."

A special section is devoted to the technic of injections, including transfusion of blood, in the treatment of tropical diseases. Medical zoology and laboratory methods are considered in the appendix which comprises more than 200 pages. The illustrations, almost without exception, are instructive and useful. The book will continue to be of practical service not only to medical students and physicians in tropical places, but to all who may be interested in the diseases with which it deals.

LEHRBUCH DER TOXIKOLOGIE FÜR STUDIUM UND PRAKIS VON FERDINAND FLURY, Professor der Pharmakologie an der Universität Würzburg, und HEINRICH ZANGGER, Professor der gerichtl. Medizin an der Universität Zürich Paper Price, 29 marks Pp 500, with 9 illustrations Berlin Julius Springer, 1928

This work is primarily intended as an introduction to the study of toxicology for students and as a short reference work for practitioners, although it should prove of interest to special workers in this field. The book is divided into two parts: the general part, in which a rather extensive discussion is given of the general principles of toxicology, statistics of poisoning and certain legal requirements in connection with poisons, and the special part, in which are handled the specific groups of poisons. The discussions in the general part are, for the most part, adequately presented, although the section dealing with the methods of detection would seem to be somewhat curtailed, especially when little or no attention is given to this field under the specific poisons. It is possible, however, that this phase of the subject may be properly shortened in a work of this character, intended for students who will, perhaps, never have occasion to make any tests for the poisons in question. The special part is well arranged and presented, the discussions being clear and concise, although special emphasis is given to symptomatology and treatment. Especially commendable in this part is the section by Zangger dealing with the gaseous poisons. The subject matter in this special part is presented and arranged in such a manner that the student should have little difficulty in correlating and assimilating it. This book should prove a valuable addition to the library of those who wish a short work on the subject.

CONSTITUTIONAL INADEQUACIES By NICOLA PENDE, M.D. Translated by SANTE NACCARATI, M.D., Sc.D., Ph.D., with a foreword by GEORGE DRAPER, M.D. Price, \$3.50 Pp 270 Philadelphia Lea & Febiger, 1928

A review of our present knowledge in constitutional pathology is presented in this small volume. The investigations and conceptions of the Italian School on this subject are especially stressed. After a definition of the term constitution, its three aspects (morphologic, dynamic-humoral and psychologic) are discussed. Two main constitutional types (megalosplanchnic-hypervegetative and micro-splanchnic-hypovegetative) are recognized, from which numerous variants and mixtures exist. In the second part of the book the author discusses the localized constitutional anomalies and inadequacies according to the organic systems (skin with appendages, skeletomuscular system, blood and hemolymphopoietic system, circulatory apparatus, respiratory apparatus, digestive apparatus, urogenital apparatus, nervous system and the endocrine system). A chapter dealing with the therapy of constitutional inadequacies concludes the presentation. The book illustrates very well the importance of the individual constitution in health and disease. While the conclusions reached by the author are not always convincing as they are lacking proper support by sufficient and well recognized observations and facts, the book is highly stimulating. There is no bibliography.

LECTURES ON PLANT PATHOLOGY AND PHYSIOLOGY IN RELATION TO MAN A series of lectures given at the Mayo Foundation and the Universities of Wisconsin, Minnesota and Iowa, the Des Moines Academy of Medicine, and Iowa State College in 1926 and 1927. Cloth Price, \$2.50 Pp 207, with illustrations Philadelphia W. B. Saunders Company, 1928

The subjects discussed are: filtrable viruses, by L. O. Kunkel, ecology and human affairs, by H. C. Cowles, some aspects of the problem of the fusarium, by G. H. Coones, racial specialization in the fungi of plant disease, by E. C. Stakman, the relation of plant pathology to human affairs, by H. H. Whetzel, and some aspects of cellular physiology, by W. J. V. Osterhout. The lecturers are successful investigators in their respective fields, and their presentations will interest physicians and others who are concerned in the advances of biologic science.

## Books Received

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**SURGICAL PATHOLOGY** By CECIL P G WAKELEY, FRCS (Eng), FRS (Edin), and ST J D BUNTON, MB, BS (Lond), FRCS (Eng) Price, \$12 50 Pages 904, with 392 illustrations New York William Wood & Company, 1929

**PATHOLOGY FOR STUDENTS AND PRACTITIONERS** Authorized Translation of the "Lehrbuch der pathologischen Anatomie" By DR EDWARD KAUFMANN, Professor of General Pathology and Pathological Anatomy, University of Gottingen Translated by Stanley P Reimann, MD, Pathologist and Director of the Research Institute of the Lankenau Hospital In three volumes Cloth Price, \$30 per set Pp 2,452, with 1,072 illustrations Philadelphia P Blakiston's Son & Company, 1929

**REPORT OF THE MEDICAL RESEARCH COUNCIL FOR THE YEAR 1927-1928** Price, 3 shillings Pp 165 London His Majesty's Stationery Office, 1929

**LABORATORY TECHNIQUE** The Methods Employed at St Luke's Hospital, New York By F C Wood, Karl Vogel and L W Famulener Third edition, revised and enlarged Price, \$3 75 Pp 318 New York James T Dougherty, 1929

**OLD AGE** The Major Involution The Physiology and Pathology of the Aging Process By ALDRED SCOTT WARTHIN, Ph D, MD, LL D, Professor of Pathology and Director of the Pathological Laboratories in the University of Michigan, Ann Arbor Cloth Price, \$3, net Pp 200, with 29 illustrations New York Paul B Hoeber, 1929

**ETIOLOGIE ET PROPHYLAXIE DE LA GRIPPE** Bacille de Pfeiffer virus filtrant grippal Par P DUJARRIC DE LA RIVIERE (Monographies de l'Institut Pasteur) Price, 32 francs Pp 108, with 21 illustrations Paris Masson & Cie, 1929

**A MANUAL OF HELMINTHOLOGY, MEDICAL AND VETERINARY** By H W BAYLIS, MA, D Sc, Assistant Keeper, Department of Zoology, British Museum (Natural History) Price, \$10 Pp 303, with 200 illustrations New York William Wood & Company, 1929

**PROTOZOOLOGY, A MANUAL FOR MEDICAL MEN** By JOHN GORDON THOMSON, MA, MB, Ch B, Director, Department of Protozoology, London School of Hygiene and Tropical Medicine, and Andrew Robertson, MB, Ch B, Lecturer and Milner Research Fellow in the Department of Protozoology, London School of Hygiene and Tropical Medicine Price, \$11 Pp 376, with 224 illustrations New York William Wood & Company, 1929

**ARTHRITIS AND RHEUMATOID CONDITIONS** Their Nature and Treatment By RALPH PEMBERTON, MS, MD, Physician to the Presbyterian Hospital, Philadelphia, and Associate Professor of Medicine in the Graduate Medical School of the University of Pennsylvania Price, \$5, net Pp 354, with 43 illustrations Philadelphia Lea & Febiger, 1929

## RECOVERY FROM MYOSTATIC CONTRACTURE CAUSED BY TETANUS TOXIN\*

STEPHEN RANSON

AND

S W RANSON

CHICAGO

Tetanus toxin when injected into one limb of a cat, rabbit or rat causes a shortening of the extensor muscles of that leg. The leg is held rigidly extended. In from five to seven days after the injection, if the dose has been an adequate one, the extensor muscles become set at this shortened length and fail to relax even after section of the motor nerves. The muscles are in a condition of myostatic contracture<sup>1</sup>. We have seen tetanic contracture in the quadriceps femoris of the cat persist for as many as five days after section of the femoral nerve, disappearing gradually as atrophy set in<sup>2</sup>. If the nerves have not been cut and if the dose has been just a little less than would produce generalized tetanus, the contracture may persist in rabbits for months. In the rat and particularly in the guinea-pig, in which the susceptibility is greater and the margin between the dose of toxin producing local tetanus and that causing a fatal general tetanus is less, it has been the experience in the laboratory that recovery from local tetanus quite regularly occurs within from four to eight weeks.

It might be inferred from this that a muscle in the myostatic contracture caused by tetanus toxin had not been irreparably damaged. But there is no evidence recorded to show that, in those animals that recover, the local tetanus had ever progressed to the stage of myostatic contracture. The experiments recorded in this paper were undertaken to determine the extent to which a muscle after it has once been set in contracture by the action of tetanus toxin may regain its normal length, structure and function.

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\* Submitted for publication, Jan 15, 1929

\* From the Institute of Neurology, Northwestern University Medical School

<sup>1</sup> Ranson, S W, and Morris, A W. *J Comp Neurol* **42** 99, 1926  
Ranson, S W, and Sams, C F. *J Neurol & Psychopath* **8** 304, 1928. Davenport, H K, Ranson, S W, and Stevens, E. *Microscopic Changes of Muscle in Myostatic Contracture of Local Tetanus*, Arch Path, this issue, p 978

<sup>2</sup> Ranson, S W. *Local Tetanus, A Study of Muscle Tonus and Contracture*, Arch Neurol & Psychiat **20** 663 (Oct) 1928

## METHOD

In order to be sure that myostatic contracture had developed, it was not sufficient to place the animal under deep anesthesia. Only if the muscle failed to relax after section of the motor nerve or after the death of the animal could one be sure that nerve impulses were not responsible for the maintenance of the shortened state. But these conditions excluded the possibility of studying the recovery of the muscle. To meet this difficulty, it was decided to work with pairs of rats. One of each pair, as control, was put to death at the height of contracture, the other was allowed to live for several weeks or months and then was killed in order that the muscles might be studied and the extent of recovery determined.

Young adult rats were used and were paired according to weight, the two members of a pair coming within 10 Gm of being the same weight. The toxin used was of such a strength that 0.25 cc constituted a suitable dose, and this amount was injected into the muscles on the back of the right thigh in each rat. Although the amount injected was greater than in the experiments of Davenport, Ranson and Stevens<sup>1</sup> the toxin was much weaker and the actual dose less and the contractures produced were less pronounced. The dose was necessarily somewhat below that required to produce the most pronounced contracture because it was essential to keep the animals alive until recovery occurred.

A number of the rats died of tetanus and five others lost their identification tags. Seven pairs were carried through to the completion of the experiment. The data in regard to these are given in the accompanying table.

The five that lost their identification tags weeks or months after the injection were roughly paired according to their weight at the end of the experiment with five others that had been killed at the height of the contracture. The data obtained from this group agreed in all essentials with the data obtained from the better controlled experiments recorded in the table.

When the rigidity was at its height from seven to thirteen days after the injection, the rats were anesthetized deeply with ether and the amount of relaxation of the right hind leg was tested. One rat of each pair was allowed to recover from the anesthetic and the other was killed. Immediately after the death of the latter, the amount of relaxation of its right leg was again tested. Then the gastrocnemii of both hind legs were removed and fixed under a tension of 50 Gm in a diluted solution of formaldehyde U S P (1:10). After fixation the weight and length of the muscles and the length of an easily identifiable bundle of parallel muscle fibers in each was determined, and histologic sections were prepared according to the methods described by Davenport, Ranson and Stevens<sup>1</sup>.

After recovery had occurred, the surviving members of the pairs were treated in a similar manner.

## RESULTS

All the rats developed typical local tetanus in the leg into which injections were made and a contracture in the gastrocnemius which failed to relax completely under deep ether anesthesia. For example, the pair listed last in the table was anesthetized thirteen days after the injection. In both rats, when under deep anesthesia, the right ankle could be flexed to a right angle. One rat was killed, and after death the ankle could still be flexed only to a right angle. Sixty-two days later (seventy-five days after the injection), the other rat had fully recovered and was using the right leg as well as the left. But when this rat was

placed under deep anesthesia, the ankle joint moved freely until it was almost completely flexed, then resistance was encountered. This persisted after the death of the animal and even after the section of the achilles tendon. It was therefore due to changes in the ankle joint.

As shown in the table, the right gastrocnemii of the rats killed in from seven to thirteen days after injection were consistently shorter than the left control muscles. The average length of the seven left gastrocnemii was 27.8 mm and of the seven right gastrocnemii 24.2 mm, representing an average shortening of 3.6 mm. On the other hand, the rats killed from fifty-six to 110 days after the injection had right gastrocnemii of approximately the same length as the left. This shows that, with time and a return to normal function, the shortened muscles returned again to approximately normal length.

In the rats killed from seven to thirteen days after the injection, the individual muscle fibers selected for measurement were, on the average, 3 mm shorter in the muscles on the injected side than in the control

*Measurements of the Gastrocnemius Muscle of the White Rat in the Contracture of Local Tetanus and After Recovery*

During Contracture					After Recovery				
Days After Injection	Length of Muscle, Mm		Length of Fibers, Mm		Days After Injection	Length of Muscle, Mm		Length of Fibers, Mm	
	Normal	Injected	Normal	Injected		Normal	Injected	Normal	Injected
7	26.0	23.8	10.0	6.8	66	28.5	27.5	10.9	7.7
7	27.2	23.0	10.6	6.7	86	29.6	31.1	11.2	9.0
9	39.2	25.2	10.5	6.7	53	26.0	25.5	9.4	9.0
10	27.6	24.1	9.1	5.2	59	25.2	25.9	9.0	7.9
11	27.8	22.9	9.0	4.7	61	31.0	28.8	10.0	7.1
12	26.9	24.8	8.0	7.0	110	27.0	27.0	9.2	7.8
13	29.0	26.0	9.1	8.5	75	27.4	27.2	9.9	7.8
Average	27.8	24.2	9.5	6.5	Average	27.8	27.6	9.9	8.0

muscles. In the rats killed from fifty-six to 110 days after the injection, the muscle fibers of the right gastrocnemii were, on the average, 1.9 mm shorter than the same fibers in the control muscles of their left legs.

It is a little difficult to understand how, on recovery from contracture, the muscles could have returned so nearly to their normal length and still have the individual muscle fibers showing an appreciable amount of shortening. It could be explained on the assumption that during the three weeks or more when the muscle was under continuous tension, before the tetanus subsided, the thin intramuscular fibrous septums became slightly stretched.

When the five rats that lost their identification tags were paired with five others of approximately the same weight the five pairs thus obtained gave essentially the same results as the seven included in the table.

It is evident from these results that a muscle may recover from the myostatic contracture due to tetanus toxin so that the limb of which it forms a part can be used in a normal manner. The length of the muscle also returns approximately to normal, but some shortening of the individual muscle fibers remains.

The weight of the muscle was not altered by tetanic contracture in the animals killed from seven to thirteen days after the injection. But, in the animals that had recovered from the contracture, there was some slight atrophy of the muscle on the side which received the injection. This weighed, on the average, 0.96 Gm., as compared with 1.13 Gm. for the control muscle.

Histologic sections of the muscles were made and stained in the manner described by Davenport, Ranson and Stevens, except that all the material had been fixed in formaldehyde. The muscles that had been fixed at the height of contracture, from seven to thirteen days after the injection, showed the blurring of cross striations described by Davenport, Ranson and Stevens<sup>1</sup>. The individual myofibrils were more evident than in normal muscle, but were less tightly bound together and more tortuous (figs *A* and *C*). Irregular patches of light staining, due to a decrease in the affinity of the anisotropic disks for the various dyes, also formed a conspicuous part of the picture. Nuclear proliferation was less marked than in the preparations described by Davenport, Ranson and Stevens, but a few tubes of sarcolemma, filled with nuclei and representing degenerating muscle fibers, were seen. In transverse sections vacuoles could be seen in a few of the muscle fibers.

It is evident that the contractures produced in this investigation were not of such high grade as those investigated by Davenport, Ranson and Stevens<sup>1</sup>. The histologic changes were not as advanced, and there was less shortening of the muscles. Their results could not be duplicated in this investigation because the larger doses of toxin that they employed would, after two or three weeks, have caused the death of the animal, thus preventing the study of recovery. Nevertheless, the histologic changes, as well as the shortening, showed that the muscles were in myostatic contracture.

The muscles, which in from fifty-six to 110 days after the injection had recovered from the contracture and returned to approximately normal length, were of normal histologic appearance. The cross striations were regular and well defined (figs *B* and *D*). The myofibrils were no longer abnormally prominent and the irregular, patchy staining had disappeared. The nuclei were normal in number and arrangement and the long masses of nuclei, representing degenerating fibers, were not seen. It is not possible to say whether these muscle fibers had regenerated or been replaced by connective tissue. It was not possible to see that there was any increase in connective tissue, and if any increase had occurred, it must have been slight.





*A* a longitudinal section of the gastrocnemius muscle in myostatic contracture caused by tetanus toxin,  $\times 570$  *B*, a longitudinal section of the gastrocnemius muscle after recovery from myostatic contracture,  $\times 570$  *C*, a longitudinal section of the gastrocnemius muscle in myostatic contracture caused by tetanus toxin  $\times 400$  *D*, a longitudinal section of the gastrocnemius muscle after recovery from myostatic contracture,  $\times 400$

## CONCLUSION AND SUMMARY

The gastrocnemius muscle of the white rat, which has been set at a shortened length in the myostatic contracture of local tetanus, may after from eight to twelve weeks recover approximately its normal length and be used again normally in locomotion. The muscle acquires again a normal histologic appearance. The muscle fibers show regular and well defined cross striations and nuclei of the normal number and distribution. There is no obvious increase in connective tissue.

# A MORPHOLOGIC STUDY OF REGENERATION OF THE LIVER AFTER PARTIAL REMOVAL\*

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The real meaning of "regeneration" is restoration of tissue or of a part of an organ at the site of its removal, and the term implies compensation, either structural, as of a part, or physiologic, as of a function. In the restoration of hepatic tissue after partial hepatectomy, the replacement does not occur at the stump from which the lobes were removed, but within the remaining lobes, so that "restoration" or "restitution" might describe the process more accurately. This process, however, has been known as "regeneration" in the medical literature, and so it would be confusing to offer a different title.

The idea of regeneration of the liver comes down from antiquity, first revealing itself in the myth concerning Prometheus, whose liver was gnawed on daily by the tormenting vulture at the behest of Jove. The first scientific observers to suggest the possibility of regeneration of the liver were Cruveilhier<sup>1</sup> and Andral<sup>2</sup>. Since then, this conception has been widely accepted but with considerable divergence of opinion as to the manner and the extent of the process. Albers<sup>3</sup> and Weismann<sup>4</sup> were unconvinced of any regenerative capacity, and Aschoff<sup>5</sup> stated that the reformation of any organ was never marked, least of all that of a glandular organ.

The literature on the regeneration of the liver is exceedingly comprehensive, surveying the process thoroughly from the aspects of both clinical and experimental pathology. The following men have contributed relatively complete reviews of it: von Podwyssozki,<sup>6</sup> von

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\* Submitted for publication, Feb 12, 1929

<sup>1</sup> From the Division of Experimental Surgery and Pathology, The Mayo Foundation

1 Cruveilhier, J, quoted by Milne, L S. The Histology of Liver Tissue Regeneration, *J Path & Bact* **13** 127, 1909

2 Andral, quoted by Melchior, Eduard. Ein Beitrage zur alkoholischen hypertrophischen Cirrhose (Hanot-Gilbert) mit besonderer Berücksichtigung der Regenerationsvorgänge des Leberparenchyms, *Beitr z path Anat u z allg Path* **42** 479, 1907

3 Albers, quoted by Melchior (footnote 2)

4 Weismann, A, quoted by Milne (footnote 1)

5 Aschoff, L. Regeneration und Hypertrophie, *Ergebn d allg Path u path Anat* **5** 22, 1898

6 Von Podwyssozki, W, Jr. Experimentelle Untersuchungen über die Regeneration der Drüsengewebe. *Beitr z path Anat u z allg Path* **1** 259, 1886

Meister,<sup>7</sup> Meder,<sup>8</sup> Barbacci,<sup>9</sup> MacCallum,<sup>10</sup> Melchior,<sup>11</sup> Muir,<sup>12</sup> Milne,<sup>13</sup> Hess,<sup>14</sup> Herxheimer and Garlach<sup>15</sup> and Schultz, Hall and Baker<sup>16</sup>

#### CLINICAL PATHOLOGY

Regeneration of the liver has been studied whenever any rapid, widespread destructive lesion of this organ has occurred. The favored lesions have been acute and subacute yellow atrophy because of the speed and vigor with which in these conditions destruction of hepatic cells takes place.

Marchand<sup>17</sup> was the first accurately to describe acute yellow atrophy and the subsequent regeneration from the injured hepatic cells. These, he said, gave rise to new cells. The apparent proliferation of the ends of small bile ducts was due to either degeneration or regeneration and rearrangement of the injured parenchymal cells. He stated definitely that the bile ducts did not proliferate, and did not form new hepatic cells. His description of acute yellow atrophy, however, remains as authoritative as when he wrote it.

Meder,<sup>8</sup> confirming Marchand's work, pointed out that the evidence of proliferation of the bile ducts was most marked when the destruction

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7 Von Meister, Valerian. *Recreation des Lebergewebes nach Abtragung ganzer Leberlappen*, Beitr z path Anat u z allg Path **15** 1, 1894.

8 Meder, E. *Ueber acute Leberatrophie mit besonderer Berücksichtigung der dabei beobachteten Regenerationserscheinungen*, Beitr z path Anat u z allg Path **17** 143, 1895.

9 Barbacci, O. *Ueber Ausgang der acuten Leberatrophie in multiple, knotige Hyperplasie*, Beitr z path Anat u z allg Path **30** 49, 1901.

10 MacCallum, W. G. *Regenerative Changes in the Liver After Acute Yellow Atrophy*, Johns Hopkins Hosp Rep **10** 375, 1902, *Regenerative Changes in Cirrhosis of the Liver*, J A M A **43** 649 (Sept 3) 1904.

11 Melchior, Eduard. *Ein Beitrag zur alkoholischen hypertrophischen Cirrhose (Hanot-Gilbert) mit besonderer Berücksichtigung der Regenerationsvorgänge des Leberparenchyms*, Beitr z path Anat u z allg Path **42** 479, 1907.

12 Muir, Robert. *On Proliferation of the Cells of the Liver*, J Path & Bact **12** 287, 1908.

13 Milne, L. S. *The Histology of Liver Tissue Regeneration*, J Path & Bact **13** 127, 1909.

14 Hess, Otto. *Ueber die bei akuten gelben Leberatrophie auftretenden Regenerationsprozesse*, Beitr z path Anat u z allg Path **56** 22, 1914.

15 Herxheimer, Gotthold, and Garlach, Werner. *Ueber Leberatrophie und ihr Verhältnis zu Syphilis und Salvarsan, zugleich ein Beitrag zur Frage der Leberzellregeneration*, Beitr z path Anat u z allg Path **68** 93, 1921.

16 Schultz, E. W., Hall, E. M., and Baker, H. V. *Repair of the Liver Following the Injection of Chloroform into the Portal Vein*, J M Research **44** 207, 1923.

17 Marchand, F. *Ueber Ausgang der acuten Leberatrophie in multiple knotige Hyperplasie*, Beitr z path Anat u z allg Path **17** 206, 1895.

of the hepatic cells was most severe. The budding at the end of the bile ducts was true proliferation, and not degeneration of hepatic cells, as Maichand had believed. In one of his five cases, Meder found mitotic figures in the buds of the bile duct continuous with new hepatic cells. He concluded that when the destruction of the tissue of the liver had been severe, the bile ducts participated in the formation of new hepatic cells.

Ribbert<sup>18</sup> agreed with Maichand that the bile ducts did not proliferate or form new hepatic cells, and that the regeneration was from remaining cell strands. Carraro<sup>19</sup> believed that there was proliferation of the bile ducts, but that these duct beds never became hepatic cells. Stroebe<sup>20</sup> maintained that if a sufficient amount of hepatic tissue were destroyed, the interlobular bile ducts would sprout and form new hepatic cells. Barbacci<sup>9</sup> agreed with Stroebe, believing that if injured hepatic cells remained, they divided, but that otherwise the embryonic manner of regeneration prevailed, namely, that the interlobular epithelium of the bile duct proliferated and formed new hepatic cells.

MacCallum<sup>10</sup> (1902) found mitotic figures in the tips of proliferating bile ducts. The presence of bile in the drainage capillaries indicated functional activity of the new hepatic cells. He noted the distortion of the new lobules. And finally, if all the parenchymal cells were destroyed, the bile duct cells would multiply and differentiate, adopting the characteristics of hepatic cells. On the other hand, if any of the hepatic cells remained, they gave rise to new hepatic cells and the bile ducts took little or no part in the process.

Milne<sup>13</sup> offered another interpretation of the bile duct buds. They were the hardy, persistent interlobular canaliculi which became embedded in the new connective tissue, and served to connect the remaining or regenerating hepatic cells with larger bile ducts. Rarely, these ducts might show a meager, local proliferation along their course, but new hepatic cells did not arise from them. Hepatic tissue was restored by direct division of the remaining hepatic cells.

Latei, Hess<sup>14</sup> reviewed this aspect of regeneration in acute yellow atrophy and agreed with MacCallum, except that he believed the epithelium of the bile duct and injured hepatic cells was equivalent for purposes of regeneration. More recently, Herxheimer and Garlach<sup>15</sup> have shown this with fine serial sections.

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18 Ribbert, quoted by Hess (footnote 14) and by MacCallum (footnote 10)

19 Carraro, quoted by Hess (footnote 14)

20 Stroebe, H. Zur Kenntnis der sogenannten acuten Leberatrophy, ihrer Histogenese und Aetiologie mit besonderer Berücksichtigung der Spätstadien, Beitr. z. path. Anat. u. z. allg. Path. **21** 379, 1897

In the different types of atrophy of the liver there are many hyperplastic nodules which represent varying degrees of regeneration, dependent on the duration of the atrophy. M'Donald and Milne<sup>21</sup> maintained that the hyperplastic, nodular foci arose only from the uninjured hepatic cells and not from the bile ducts. Miller and Rutherford<sup>22</sup> reported sixteen cases of atrophy of the liver in which the budding at the ends of the bile duct, with enlargement of nuclei and frequent mitosis, was the first evidence of regeneration.

Hess<sup>23</sup> observed new hepatic cells regenerating from the epithelium of the bile duct in three cases of rupture of the liver, and contrasted it with the embryonic process. He did not see any mitotic figures, but his cases were of several days' duration. Mun<sup>12</sup> described three similar cases, which showed ductlike structures growing from the ends of trabeculae. He believed this proliferation to be an attempt of the hepatic cells to repair a breach in the continuity of the duct system.

Regeneration of the liver has been observed in cirrhosis and carcinoma of the liver<sup>24</sup>. The question of carcinoma arising from the hyperplastic nodules in cases of cirrhosis has long been discussed. Many primary hepatic neoplasms are associated with cirrhosis.

MacCallum<sup>10</sup> (1904) noted the similarity of regeneration in cirrhosis and subacute yellow atrophy. The remaining hepatic cells divided by mitosis and the bile ducts penetrated the scar tissue, sending forth buds, which became hepatic cells<sup>25</sup>. The epithelium of the bile duct was more resistant than the hepatic cell, but both types of cells participated equally in regeneration.

So-called compensatory regeneration of the liver has also been noted in suppurative hydatid cysts, echinococcus cysts, syphilitic obliteration of vessels to one lobe and in chronic venous congestion<sup>13</sup>.

Mention should be made of the opinions on division of hepatic cells. Prior to the recognition of karyokinesis, these cells were supposed to divide by amitotic, or direct, division. Tillmanns<sup>26</sup> observed mitotic figures in hepatic cells near scars, interpreting them as evidence of

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21 M'Donald, Stuart, and Milne, L. S. Subacute Liver Atrophy, *J. Path. & Bact.* **13** 161, 1909.

22 Miller, James, and Rutherford, Andrew. Liver Atrophy, *Quart. J. Med.* **17** 81, 1923.

23 Hess, Karl. Beitrag zur Lehre von den traumatischen Leberrupturen, *Virchows Arch. f. path. Anat.* **121** 154, 1890.

24 Milne, L. S. Primary Epithelial Tumour Growth in the Liver, *J. Path. & Bact.* **13** 348, 1909.

25 MacCallum, W. G. Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1917, p. 305.

26 Tillmanns, H. Experimentelle und anatomische Untersuchungen über Wunden der Leber und Niere. Ein Beitrag zur Lehre von der antiseptischen Wundheilung, *Virchows Arch. f. path. Anat.* **78** 437, 1879.

regeneration Ziegler and Obolonsky<sup>27</sup> noted mitosis after phosphorus poisoning Bizzozero and Vassale<sup>28</sup> observed mitotic figures in the livers of animals, and regarded them as evidence of physiologic replacement

Balbani and Henneguy<sup>29</sup> described amitotic and mitotic division of cells in the same specimen Adler<sup>30</sup> noted both amitosis and mitosis in cases of phosphorus poisoning and eclampsia Von Podwyssozki<sup>6</sup> and Ponfick<sup>31</sup> described mitosis in regenerating liver Milne<sup>13</sup> and Miller and Rutherford<sup>22</sup> believed that the division was chiefly by amitosis Whipple and Sperry<sup>32</sup> found mitotic figures after prolonged chloroform anesthesia, usually most numerous on the second day Schultz, Hall and Baker<sup>16</sup> observed only a few mitotic figures, but believed this to be the prevalent mode of division because of lack of evidence of direct division Maximow<sup>33</sup> found hepatic cells dividing by mitosis under conditions of tissue culture

#### EXPERIMENTAL PATHOLOGY

Experiments in this field were first conducted in Italy Colucci<sup>34</sup> injured the continuity of the liver in guinea-pigs and noted new hepatic cells, which he believed arose from leukocytes by nuclear division Corona<sup>35</sup> and Tizzoni<sup>36</sup> observed the proliferation of hepatic cells and believed it due to direct mechanical action causing division of the cells Griffini<sup>37</sup> noted the transformation of cords of epithelial cells into small hepatic cells to form a new trabecular system The epithelium to which

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27 Ziegler, E, and Obolonsky, N Experimentelle Untersuchungen über die Wirkung des Arseniks und des Phosphors auf die Leber und die Nieren, Beitr z path Anat u Physiol **2** 291, 1888

28 Bizzozero, G, and Vassale, G Ueber die Erzeugung und die physiologische Regeneration der Drüsenzellen bei den Säugethieren, Virchows Arch f path Anat **110** 155, 1887

29 Balbani and Henneguy, quoted by Milne (footnote 13)

30 Adler, L Ueber helle Zellen in der menschlichen Leber, Beitr z path Anat u z allg Path **35** 127 1904

31 Ponfick, E Experimentelle Beiträge zur Pathologie der Leber, Virchows Arch f path Anat, 1895, vol 138, suppl, p 81

32 Whipple, G H, and Sperry, J A Chloroform poisoning Liver Necrosis and Repair, Bull Johns Hopkins Hosp **20** 278, 1909

33 Maximow, A A Some Applications of the Method of Tissue Culture to the Solution of Pathological Problems Mayo Foundation Lectures (unpublished data)

34 Colucci, V, quoted by von Podwyssozki, Jr (footnote 6)

35 Corona, quoted by von Podwyssozki, Jr (footnote 6)

36 Tizzoni, quoted by von Podwyssozki, Jr (footnote 6)

37 Griffini, quoted by von Podwyssozki, Jr (footnote 6) and Melchior (footnote 11)

he referred was probably that lining bile ducts. Canalis<sup>38</sup> removed small blocks from the livers of dogs and guinea-pigs, and saw the proliferation of hepatic cells and a new formation of bile ducts, which, however, he did not believe arose from the bile ducts. He did not observe the transition of bile ducts to hepatic cells, as Griffin had suggested.

Von Podwyssozki<sup>6</sup> removed small wedges from the livers of rats, cats, guinea-pigs and rabbits. His work was the first carried on in accord with modern standards. Evidence of regeneration in adjacent hepatic cells appeared within twenty-four hours. In rats, mitotic figures appeared near the wound within two and a half days. Bile ducts began to sprout into the scar tissue by the fourth day, and by the tenth had become hepatic cells. Regeneration was predominantly from the bile ducts in guinea-pigs and rabbits, and from the hepatic cells in cats and rats. Pius<sup>39</sup> confirmed these results the following year.

Ponfick<sup>40</sup> removed the liver partially from rabbits and dogs, removing three or even four of the major lobes, an equivalent of 75 per cent. A three-fold increase of hepatic tissue occurred, which he attributed to functional stimulation arising from physiologic lack. The newly formed tissue functioned normally because it arose from an entirely normal substratum, in contrast with the scarred soil in which hepatic cells arose after cirrhosis. After congestion, extreme hypertrophy occurred which reached the optimum within a few weeks. The new hepatic cells were swollen and were more voluminous with pale, bright cytoplasm, and their nuclei were somewhat larger than normal. Mitosis occurred by the second day. Nuclear division frequently preceded that of the cytoplasm, which lagged behind a definite interval. The regenerating field was not uniform, being speckled with pairs of new cells, which had blossomed forth as a stately procession of crops. Eventually, these new cells became so numerous that they formed islands, penetrating the original tissue in an harmonious though despotic sequence. The vascular system regenerated rapidly, but the radial arrangement of blood vessels was supplanted by one of the cavernous type.

The epithelium of the coarser bile passages proliferated, producing an unevenness, not unlike the ruffles of a collar, by the third day. Mitosis was noted in this proliferating epithelium, which was confined to the outlines of the original system. Ponfick did not observe growth by sprouts or off-shoots of the epithelium of the bile duct. The capillaries of the bile ducts regenerated less quickly than the hepatic cells. The narrow, uneven appearance of capillaries of the bile duct in the centers

38 Canalis, quoted by Hess (footnote 14) and by Melchior (footnote 11)

39 Prus, quoted by Hess (footnote 14)

40 Ponfick, E. Ueber Leberestirpation, *Jahresb d schles Gesellsch f vaterl Kult* **67** 75, 1889, Ueber Leberresection und Leberrecreation, *Verhandl d deutsch Gesellsch f Chir* **19** 28, 1890, also footnote 31



of islands of regenerated glandular tissue he attributed to an overproduction of new gland cells or their too hasty connection with the old duct system. The ground plan remained unchanged, since regeneration occurred through interposition. The hypertrophy was built on the framework and foundation of old lobules and trabeculae. The lobules lost their former regularity and increased in all dimensions. Growth was slow at first for two days and then was accelerated, lasting three or four weeks. About the circumference of old lobules and centering always on branches of the hepatic veins were groups of new cells or excrescences which gave the lobule a cloverlike or heartlike shape.

Von Meister<sup>7</sup> corroborated Ponfick's observations. He asserted that although 75 per cent of the liver was removed, there would be restoration up to 80 per cent of the original weight, at least in rats, rabbits and dogs. Mann and Magath<sup>41</sup> also noted this in dogs. The process required from forty-five to sixty days and was more rapid in young, strong animals. Von Meister regarded it as compensatory hypertrophy of old lobules from hyperplasia of their cellular elements. Growth was subsequent to pressure outward of the increased number of cells. The old cells made way for the new and the lobules enlarged to two, three or even four times their former size. Proliferation, as indicated by mitosis, began on the second day in the peripheral zones. Cells near the centers of the lobules remained in a latent stage due to pressure from the strong growth at the periphery. The bile ducts and blood vessels did not take any special part in the process but were carried along by the hypertrophy. The remaining lobes were individual organs, each having the power of hypertrophy in case the other was extirpated.

Flock<sup>42</sup> arrived at similar conclusions. Regeneration appeared first at the periphery of the lobules and the process was completed in forty-four days. The lobular hypertrophy was compensatory and dependent on the proliferation and hypertrophy of peripheral cells. Bile ducts and blood vessels played a secondary part, simply following in the footsteps of the regenerating hepatic cells.

Mall<sup>43</sup> pointed out that the so-called hypertrophied lobules were in reality new compound lobules. The old lobules sprouted and gave rise to new lobules of normal size. The apparent hypertrophy lay in the failure to recognize the newly formed compound lobules which had arisen from the periphery of the old ones. He observed that regeneration occurred chiefly at the periphery, but that this zone corresponded

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41 Mann, F. C., and Magath, T. B. The Production of Chronic Liver Insufficiency, *Am J Physiol* **59** 485, 1922.

42 Flock, quoted by Herxheimer and Garlach (footnote 15) and by Melchior (footnote 11).

43 Mall, F. P. A Study of the Structural Unit of the Liver, *Am J Anat* **5** 227, 1906.

to the center of the portal unit. Mitosis was rare and binucleate cells common. In the livers of human beings which showed regeneration, mitotic figures were found in the region of the terminal bile ducts. Schaper and Cohen<sup>44</sup> believed that when regeneration formed typical lobules, the growth had taken place within the more minute bile ducts.

Janson<sup>45</sup> ligated the hepatic artery to various lobes of the liver in rabbits and found regeneration of those lobes with proliferation of the bile ducts within. These he called "pseudo bile ducts" and regarded them as atrophic cells of the liver. He believed that in the case of extreme regeneration, the bile ducts might give rise to hepatic cells, but he did not note such a phenomenon.

Rous and Larimore<sup>46</sup> ligated branches of the portal vein to certain lobes in rabbits and dogs and found atrophy of those lobes with hypertrophy of the others the portal circulation of which was uninjured. The atrophy was simple, that is, there was no degeneration or increase of connective tissue. Also, the atrophy was conditional, since it did not progress when hypertrophy was checked in the other lobes by ligation of their drainage bile ducts.

De Bary,<sup>47</sup> working on dogs, excised portions of the liver and noted the metamorphosis of the trabeculae of the cells occurring in small, dark, ductlike structures. Porcile<sup>48</sup> injected turpentine into the livers of rabbits and noted a proliferation of the bile ducts and a marked similarity of the new cells of the bile duct to the cells of the liver. Hayami<sup>49</sup> injected a 10 per cent solution of aleuronat in an emulsion of 6 per cent sodium chloride and found evidence of regeneration in four days. The regenerating hepatic cells he regarded as arising from sprouts from the bile ducts.

Milne<sup>13</sup> tried, among several methods, a method of partial hepatectomy which consisted in the ligation of branches of the portal vein and hepatic artery passing to certain lobes, waiting three weeks for atrophy and fibrosis, and then removing the shrunken, fibrotic lobes with less danger of hemorrhage. Regeneration began on the third day.

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44 Schaper and Cohen, quoted by Hess (footnote 14) and by Milne (footnote 13).

45 Janson, Carl. Ueber Leberveränderungen nach Unterbindung der Arteria hepatica, Beitr z path Anat u z allg Path **17** 505, 1895.

46 Rous, Peyton, and Larimore, Louise D. Relation of the Portal Blood to Liver Maintenance, a Demonstration of Liver Atrophy Condition on Compensation, J Exper Med **31** 609, 1920.

47 De Bary, quoted by Hess (footnote 14) and by Milne (footnote 13).

48 Porcile, Vittorio. Untersuchungen über die Herkunft der Plasmazellen in der Leber, Beitr z path Anat u z allg Path **36** 375, 1904.

49 Hayami, T. Ueber Aleuronathepatitis, Beitr z path Anat u z allg Path **39** 281, 1906.

in the peripheral zone, where the cells were pale and binuclear and contained abnormally bright nuclei. The normal trabeculae were converted into masses of hepatic cells four or more deep. Mitosis was rare, and there was ample evidence of direct division of cells. The lobules became enlarged and irregular in outline. He admitted that occasionally along the course of bile ducts there might be some local proliferation but denied budding or sprouting at their tips. From serial sections, he concluded that these were persistent remains of the finer bile canaliculi. The liver was capable of extreme regeneration provided sufficient reduction in parenchyma had occurred. Regeneration was chiefly compensatory and was the result of proliferation of hepatic cells and not of any transition in cell type.

Whipple and Sperry<sup>12</sup> produced varying degrees of central necrosis by prolonged chloroform anesthesia in dogs. The necrosis was central even after an Eck fistula or a ligation of branches of the hepatic artery had been performed. The liver showed complete regeneration within two or three weeks without scarring or cirrhosis. Necrotic debris was carried off by wandering cells, while the hepatic cells multiplied so rapidly by mitosis that regeneration was usually completed by the eleventh day and always within three weeks. Bile ducts did not take part in the regenerative process. If, however, a wedge was removed from the surface of the liver when the chloroform was administered, the ducts in the adjacent areas would send forth buds and sprouts.

Schultz, Hall and Baker<sup>16</sup> confirmed these results. They produced peripheral necrosis by injecting chloroform into the portal veins of dogs. They found first rapid mobilization of macrophages, which removed the debris, shortly followed by early invasion of fibroblasts and vascular buds. Infection stimulated the formation of fibrous tissue leading to definite cirrhosis. Without infection, repair took place without the interference of connective tissue. Regeneration resulted from proliferation of hepatic cells and also from the newly formed epithelium of the bile ducts. Hepatic cells divided by mitosis. Presumptive evidence of direct division of cells was lacking, namely nuclear fission, and hence, although it was hard to find mitotic figures, mitosis was regarded as the usual method of cell division. The authors attached significance to the transitional type of cell connecting the proliferating bile ducts with newly formed hepatic cells. Mitotic figures were found at the tips of these sprouts. Although the transitional cell might have been a cell either of the liver or of the bile duct, they interpreted it as regenerating from the epithelium of the bile duct since such cells are a less highly differentiated type than the hepatic cell. The uninjured hepatic cells were hypertrophied and multinuclear and were laden with glycogen. Carbon tetrachloride injected into the portal vein was tried with the

production of marked central necrosis. The cirrhosis following the oral administration of carbon tetrachloride was described by Lamson and his co-workers<sup>50</sup>

Opie and Alford<sup>51</sup> showed that in dogs a diet rich in fat increased the susceptibility of the liver to necrosis following the administration of chloroform, and that a diet rich in carbohydrate had a distinctly protective action. They also noted the increased toxicity of phosphorus in animals on a diet of meat as contrasted with animals on a diet of either carbohydrate or fat.

Davis and Whipple<sup>52</sup> produced central necrosis in the livers of dogs by giving chloroform either as an anesthetic or subcutaneously, and found that regeneration occurred most rapidly on a diet rich in carbohydrate or an ordinary diet of mixed foods. Regeneration was as rapid on a diet of fat as during fasting. Later it was shown that a diet wholly of meat was the equal of a diet rich in carbohydrate in hastening regeneration. After a diet rich in carbohydrate or in protein, in the order of respective efficiency for regeneration came a standard diet, then a diet rich in fat and finally fasting. Moise and Smith<sup>53</sup> verified this work and investigated the toxicity of chloroform and the degree of necrosis with varied diets. They found chloroform most toxic to an animal on a diet rich in fat, and relatively less so to an animal on a standard diet, a diet rich in carbohydrate or a diet rich in protein, in the order named. Repair consisted in the mobilization of leukocytes and the clearing away of debris, accompanied by active regeneration of the cells of the liver, which divided by mitosis.

Bell<sup>54</sup> described regeneration in the livers of dogs when atrophy had first been produced by ligation of the common bile duct, and subsequently had been counteracted by relief of the obstruction by cholecystogas-

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50 Lamson, P. D., Gardiner, G. H., Gustafson, R. K., Maire, E. D., McLean, A. J., and Wells, H. S. Pharmacology and Toxicology of Carbon Tetrachloride, *J. Pharmacol. & Exper. Therap.* **22** 215, 1923, Lamson, P. D., and Wing, Raymond. Early Cirrhosis of the Liver, Produced in Dogs by Carbon Tetrachloride, *J. Pharmacol. & Exper. Therap.* **29** 191, 1926.

51 Opie, E. L., and Alford, L. B. The Influence of Diet on Hepatic Necrosis and the Toxicity of Chloroform, *J. A. M. A.* **62** 895 (March 21) 1914, Influence of Diet on the Toxicity of Substances Which Produce Lesions of the Liver or the Kidney, *J. A. M. A.* **63** 136 (July 11) 1914.

52 Davis, N. C., and Whipple, G. H. Liver Regeneration Following Chloroform Injury as Influenced by Various Diets, *Arch. Int. Med.* **23** 711 (June) 1919, Liver Regeneration Following Chloroform Injury as Influenced by the Feeding of Casein or Gelatin, *Arch. Int. Med.* **27** 679 (June) 1921.

53 Moise, T. S., and Smith, A. H. Diet and Tissue Growth. The Regeneration of Liver Tissue on Various Adequate Diets, *J. Exper. Med.* **40** 13, 1924.

54 Bell, L. P. The Preoperative Preparation and Surgical Treatment of Carcinoma of the Pancreas with Common Duct Obstruction, *California & West Med.* **25** 503, 1926.

trostomy He found the degree of destruction of parenchymal cells and the extent of proliferation of connective tissue roughly proportional to the duration of obstruction of the common duct The interlobular capillaries of the bile ducts were stimulated to growth by the dammed-up bile and the increased intrabiliary pressure With the relief of obstruction, new hepatic cells arose from the undifferentiated bile capillaries and pushed out radially from the peribiliary spaces to form trabeculae with the uninjured hepatic cells Within two months, the parenchyma of the liver was again normal except for a slight excess of capillaries in the bile ducts

#### METHODS OF EXPERIMENTATION

Dogs were chosen for this work because they tolerated the operation well and because an anatomic conformation of the lobes of the dog's liver made removal relatively simple The animals were kept fasting for twenty-four hours before operation, but water was not withheld The abdomen was shaved, the skin was cleansed with benzine and with two coats of 2 per cent iodine in ether All operating was done under general anesthesia

*Operative Procedure*—The operator stood on the right Through a median line incision from the tip of the xiphoid to just below the umbilicus, a self-retaining retractor was inserted The left lateral lobe was delivered, and the left coronary ligament severed as the assistant retracted the costal margin The assistant grasped the pylorus and duodenum in a moist towel with the left hand and exerted gentle even traction downward and to the left The other lobes were separated from the fragile folds of the peritoneum

The lobes to be removed were lifted in the left hand and clamped across the pedicle as close to the portal vein as possible A second clamp (Fenger 17-inch [1778 cm] curved hemostat) was applied just above the first clamp, being inserted from the opposite side The cystic duct was held in a mosquito clamp to prevent spilling bile The abdominal cavity was packed off with gauze The lobes were grasped firmly to prevent oozing and were severed close to the upper clamp with a scalpel The pedicle was doubly ligated with linen tape and linen thread doubled The lower clamp was released as the first ligature was applied The upper clamp remained in place until the abdomen was sponged free of clot, to guard against slipping If the small papillary projection of the caudate lobe, lying behind the left central lobe, showed signs of impaired circulation (discoloration or tenseness), it was removed The peritoneum was dissected from its surface and two curved clamps were applied close to the portal vein The lobe was severed above the clamps and ligated as before All fragments of liver were carefully wiped from the pedicles The abdomen was closed in the routine manner the peritoneum with linen, the deep and superficial fascia with number 2 iodized catgut, and the skin with linen The incision was covered with a single thickness of gauze and painted with collodion

Extirpation of two thirds of the liver gave the greatest impetus to regeneration McMaster and Rous<sup>5</sup> showed that the left lobes (left lateral and left central) and the gallbladder lobe (right central) together represented from 65 to

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55 McMaster, P. D., and Rous, Peyton The Biliary Obstruction Required to Produce Jaundice, *J Exper Med* **33** 731, 1921

70 per cent of the average dog's liver. These lobes and the papillary projection of the caudate lobe were the ones usually selected for removal.

The average weight of the liver was from 3 to 4 per cent of the body weight with an average of 3.4 per cent. In a series of 500 necropsies, Hardenbergh<sup>56</sup> found the weight of the liver to be 4 per cent of the body weight. The variation depends on the age, sex, size of the dog, the length of hair, the breed, general health and diet. By exposing the intact liver below the costal margin at operation, a more accurate estimate of the normal weight could be made. The lobes to be removed were contrasted carefully with the whole liver, the percentage relationship was noted, and then the lobes removed were weighed. Such estimates fell within from 3 to 4 per cent of body weight. These weights were checked against the actual weights of the livers in the cases of death from hemorrhage after injury to the portal vein. A constant relationship does not exist among the various lobes of the liver. In general the left lateral lobe was the largest and the right central next in size. The other lobes varied even more in their relation to each other.

Mason and Davidson<sup>57</sup> showed that death from autolytic peritonitis ensued after small pieces of liver had been left free in the abdomen. Care must be taken to leave the abdomen clean of all pieces of liver. When the papillary projection of the caudate lobe was left with impeded circulation, the dogs died in like manner. Necropsy showed this lobe to be pale yellow, friable and conspicuously marked. Occasionally, there was local necrosis and hepatitis.

An increased tendency to bleed was not observed after partial hepatectomy. The blood clotted as rapidly after excision of part of the liver as before. Transient jaundice sometimes appeared shortly after operation, lasting from two to five days and then disappearing spontaneously. Congestion sufficient to collapse the capillaries of the bile ducts temporarily may have produced this. And also the congestion may have affected the hepatic cells, thus hindering the removal of bile pigment from the blood.

The dogs were explored at varying intervals and specimens removed from various parts of the remaining lobes. The sections removed were small wedges. Hemorrhage was controlled with figure-of-eight through-and-through sutures of fine catgut, which brought the edges together.

Further tissue was removed after regeneration had become marked, to secure specimens from the centers of lobes and also to subject the remaining portion to the stimulus for further growth. The technique employed in removing more tissue was the same as that used in removing single lobes from the normal animal.

The animals were killed under ether anesthesia by bleeding from the femoral vessels. The livers were weighed and sections taken from both the surface and the interior of the lobes.

All sections were fixed in Zenker's fluid and a diluted solution of formaldehyde, U.S.P. (1:10). Zenker's fluid gave better results. The sections were stained as a routine with iron hematoxylin and eosin. The sections stained for glycogen were fixed in absolute alcohol and stained with Best's carmine. Those which were stained for fat were fixed in the solution of formaldehyde and stained with scarlet red (Michaelis').

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56 Hardenbergh. Personal communication.

57 Mason, E. C., and Davidson, E. C. Study of Tissue Autolysis in Vivo, Blood Changes Physical and Chemical, *J. Lab. & Clin. Med.* **10**: 622, 1925.

# RESULTS

The restoration of the liver was completed in from six to eight weeks after partial hepatectomy and consisted in hypertrophy of the remaining lobes. This hypertrophy was downward and to the right, filling the right hypogastrium and protruding below the costal margin. The stomach usurped the position of the ablated lobes, displacing the remnant to the right. At first, the surface was glistening, moist and tense, indicative of the congestion within. The edges were rounded, blunt and devoid of notches. The surfaces became flattened, and were yellowish brown instead of the normal reddish brown.

The remaining lobes participated in the hypertrophy in proportion to their relative sizes. By the end of two weeks the remaining portion of



Fig 1—A regenerating liver (left), consisting of one lobe, contrasted with a normal liver (right), both dogs weighing the same (10 Kg.)

the liver approximated, in both weight and volume, four fifths of the original organ. The hypertrophy was more rapid when large amounts of tissue were removed. The weight and volume, however, were much the same at the end of eight weeks whether much or little had been extirpated (figs 1, 2 and 3).

After the liver had been pared down to one lobe by repeated hepatectomy, technical difficulties, concerned with hemostasis alone prevented indefinite continuation of the process. This regenerative capacity seemed infinite, since the liver tended to regain its normal weight and volume after each partial hepatectomy (figs 4, 5 and 6).

The liver was extremely congested for from three to five days after operation. The sinusoids were engorged with an excessive blood flow, the equivalent of the supply to the intact liver. This congestion tended

to collapse the terminal bile ducts and may account for the transient jaundice, which disappeared with subsidence of the congestion

The hepatic cells were swollen, and their pallid cytoplasm was laden with vacuoles. The nuclei were hypertrophic and filled with increased amounts of chromatin. Mitosis in the prophase was noted on the second



Fig 2—A regenerating liver (left) contrasted with the similar lobe (right lateral) of a normal liver (right)



Fig 3—A regenerating liver (center) consisting of right lateral and caudate lobes contrasted with a normal liver (right), and normal right lateral and caudate lobes (left), all from dogs weighing 10 Kg

day. The nuclear membrane and nucleolus were fading, to be replaced by chromatin material arranged in either a thread or a series of fine dots, depicting the spireme in cross-section. By the third day, mitotic figures were seen throughout the lobules, but most frequently in the peripheral



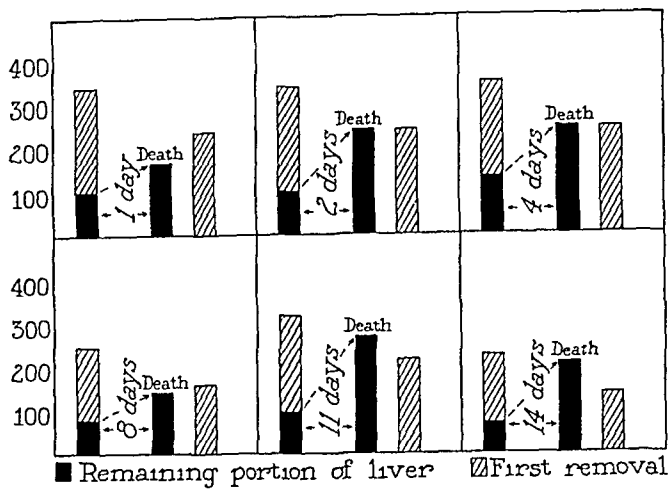


Fig 4—The rapidity and extent of the regeneration in from one to fourteen days is shown

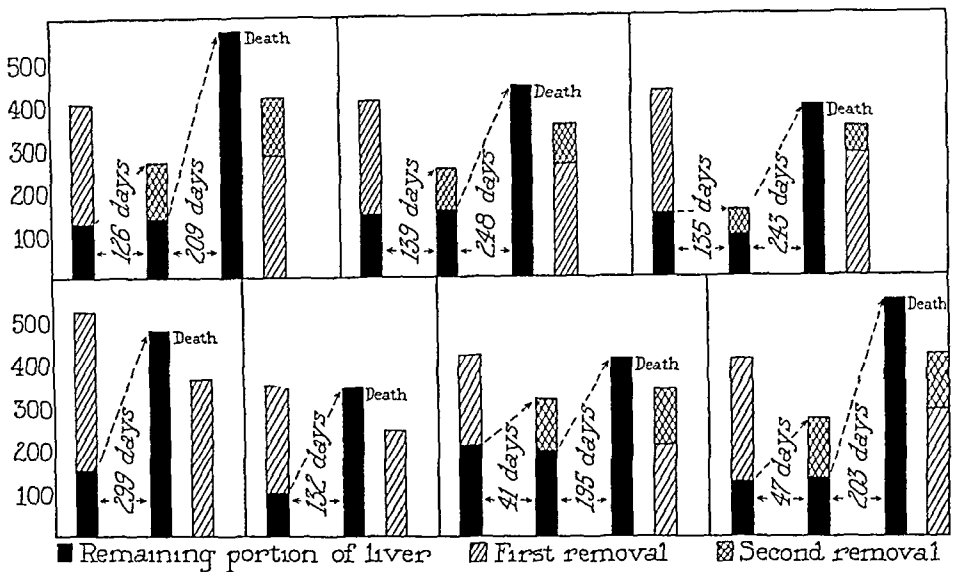


Fig 5—The effect of two partial hepatectomies. The impetus to regenerate after the second partial hepatectomy is as great as after the first. The total amount of liver removed in several instances equals the original weight of the organ. The weight of the regenerated liver at death frequently reached the original weight.

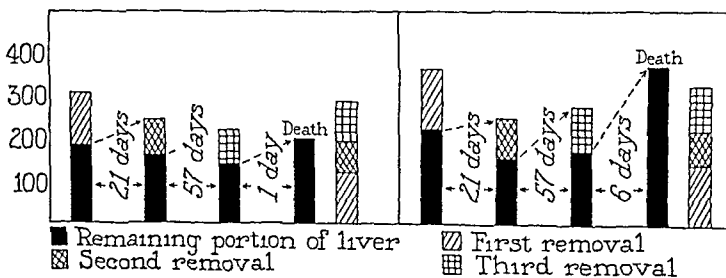


Fig 6—The effect of three partial hepatectomies. The tendency to regenerate was present after each partial hepatectomy.

zones, where growth was the most prolific (fig 7). Although the figures were never numerous, they were the most profuse from the fourth to the tenth day, and were seen as late as the fourth week.

Many binuclear cells were seen at this stage of the process. Cells undergoing nuclear fission were not observed. The nuclei divided rapidly, accompanied by the cells, some early and some later, in definite crops, which accounted for the abundance of binuclear cells shortly after regeneration began. Regeneration was so hasty that the dogs were explored or killed within the first two weeks in order that the restorative process might be observed at its peak. Although the liver reached its optimal weight and volume in two weeks, the histologic picture did not become normal until from six to eight weeks had passed.



Fig 7—A section of liver showing hepatic cells in mitosis, six days after the partial removal of the liver.  $\times 1,450$

Marked proliferation of cells occurred on the fifth and sixth days from the biliary channels in the interlobular areas. These budding areas increased rapidly in size and soon an entire section of the regenerating liver was literally studded with these cytogenic zones, which persisted as late as the sixth week (fig 8). At the ends of these budding bile ducts appeared new hepatic cells characterized by large and often double nuclei and by voluminous and more brightly staining cytoplasm. The transition from the interlobular bile ducts with their basophilic, flattened cells, out through the proliferative buds into regions of newly formed hepatic cells was extremely gradual. The hepatic cells adjacent to these buds stained more basically than normally. Just beyond these transitional cells, however, and continuous with them, were typical hepatic cells with pale pink cytoplasm.

The cells of the proliferating duct buds lacked the deep, basic staining quality associated with the epithelium of normal ducts. From the typical flattened cell of the bile ducts, with its large, dark, oval nucleus, all gradations were seen to the pale, cuboidal hepatic cell with its round nucleus. The transition from one type of cell to the other was so gradual that demarcation was not seen. Mitotic figures were not found in the buds from the ducts, although other observers reported having seen them.

On the basis of their staining reaction, their size and their nucleocytoplasmic ratio, one was impressed with their marked similarity to the adjacent hepatic cells. So pronounced was this resemblance that one must conclude that here were centers for the organization of new

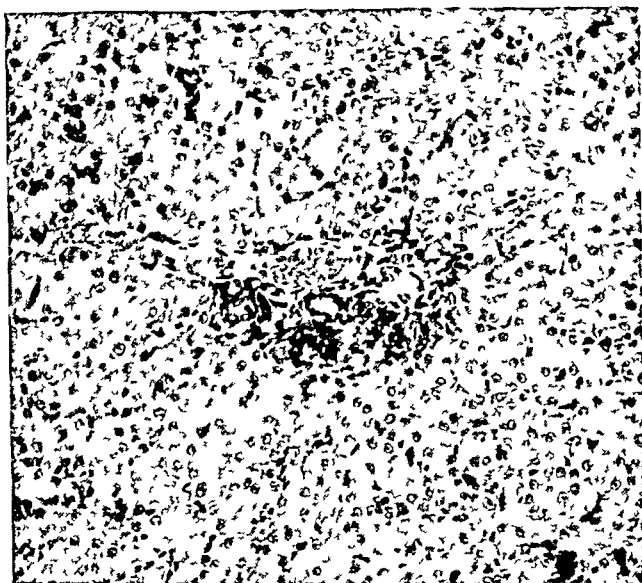


Fig 8—Proliferating bile ducts in the midst of areas of new hepatic cells six days after partial hepatectomy,  $\times 150$

hepatic lobules with their trabeculae and related canaliculi. Conclusive proof was, of course, not available within the limitations imposed on any study of fixed sections, and yet the definite budding of the bile ducts, the close similarity of the proliferated cells to those not only of biliary epithelium but of hepatic parenchyma as well, seemed to warrant the conclusion that the new hepatic lobules arise, in part, at least, from the interlobular bile ducts.

The picture was analogous to that seen in the embryonic liver in which the fetal bile ducts branch dichotomously, sending forth buds to form the parenchymal cells<sup>58</sup>. The multitudinous transitional cells so

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<sup>58</sup> Bloom, William. The Embryogenesis of Human Bile Capillaries and Ducts, *Am J Anat* **36** 451 1926

closely associated with the proliferating bile ducts seemed to indicate another source from which regenerating hepatic cells may arise. The proliferating ducts appeared as clubs and shafts of deeply staining cells with the lumina visible only here and there. Frequent examples, however, were found of ducts that were sectioned transversely.

The transitional zones and the proliferating buds faded from the third week on. Newly formed bile ducts became well defined, and hepatic cells assumed their typical appearance.

Lobules did not exceed their customary diameter (1 mm) during regeneration. Although difficult to measure on account of their irregularity of outline, a large series of photomicrographs (after from one day to 189 days) did not reveal any hypertrophy of the lobules. The old lobules gave rise to new lobules at their periphery by budding as in the fetal liver. The transitional cells, proliferating bile ducts and mitotic figures were found chiefly in the peripheral zones, where growth was most active.

The participation of the bile ducts in regeneration maintained the normal ground plan of the liver. If only the hepatic cells multiplied the lobules would have to hypertrophy to accommodate them, but this did not seem to be the case. Bile ducts proliferated and appeared to send forth shoots of transitional cells which blended with newly formed hepatic cells to preserve the normal architecture. In spite of the irregularity of lobular outline, there was sufficient similarity in contour to enable one to recognize clearly that they maintained uniformity in size during and after regeneration.

Mitosis of the hepatic cells, seen on the second day, was the first evidence of regeneration. Proliferation of the bile duct appeared on the sixth day and persisted until the sixth week. After two months, a section of regenerated liver could not be distinguished from normal liver. Rarely an interlobular bile duct was seen which had preserved its proliferated lining. The architecture was that of normal hepatic tissue and the cells were identical in every respect with normal hepatic cells.

The sinusoidal endothelium kept pace with the regenerating hepatic cells. The endothelium accompanied the newly formed hepatic cells as they attained trabeculation. Since the remnant of liver had to tolerate the blood supply of the normal liver, the growth of the endothelium might be viewed in the light of Thoma's hypothesis that an increase of blood pressure in capillary areas leads to the formation of new capillaries.

Cells of the liver, particularly those in the hyperplastic peripheral zones, were laden with glycogen from the first to the fourth week after partial removal of the liver. The glycogen occurred as large vacuoles in the clear cytoplasm of regenerating cells. Some cells appeared to

be completely filled with glycogen, their nuclei lacking or undergoing a degeneration suggestive of malnutrition subsequent to the early congestion

Immediately after operation, fat was found in large quantities, in droplets of varying sizes throughout the lobules, and was especially abundant in the marginal zones of the lobules and the peripoital connective tissue. Between the first and fourth days, the hepatic cells contained fat in small droplets. The increase occurred rapidly on the first day and continued for three days, then the fat content fell and the normal level was regained two weeks after operation.

#### COMMENT

The term "regeneration" was retained because replacement of hepatic tissue has been known by that name since reports of it first appeared in medical literature. The process does not fulfil the biologic requirements of regeneration in that replacement of the tissue removed does not take place at the site of removal. There is, however, definite restoration of lobules, the functional units of the liver, and of hepatic cells. The functioning of the liver is normal throughout the process<sup>41</sup> and there is always bile in the duodenum.

Morgan<sup>59</sup> classified regeneration as of two types, the first, "physiologic regeneration," which is the wear-and-tear sort encountered in the life cycle of an organism, and second, "restorative regeneration," which comprises the restoration of organs after their pathologic alteration. He excluded this process from either category, regarding it as one of pure hypertrophy, on the basis of Ponfick's conclusion that the lobules hypertrophy. It was suggested that this process might properly be called "compensatory hyperplasia."

The chief factor in restoration of the liver is the intense and rapid multiplication of hepatic cells. The participation of the budding bile ducts, which give rise to transitional cells and they, in turn, to new hepatic cells is, however, of definite assistance in regeneration and is chiefly responsible for the preservation of the normal histologic ground plan.

The lobes left behind at operation are the site of regeneration. They subsequently undergo marked hypertrophy since they contain the newly formed hepatic cells and lobules. The volume of these lobes, when regeneration is complete, approximates that of the original liver. The stump where a portion of the liver was removed does not show evidence of regeneration.

Cells of the liver divide by mitosis. The increased number of binuclear cells does not, alone, warrant the assumption that a direct division

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59 Morgan, T. H. *Regeneration*, New York, The Macmillan Company, 1901

of cells has occurred. Certain observers<sup>60</sup> believe this to be so because of the scarcity of mitotic figures. Conclusive evidence of amitosis (cells undergoing nuclear fission) is lacking. Although scant in numbers, sufficient mitotic figures are seen to justify the conclusion that this is the characteristic manner of division.

Ponfick, von Meister and Schultz, Hall and Baker noted the early appearance of numerous binuclear cells, filled with delicate, pale protoplasm typical of the newly formed cells. Ponfick suggested that the cells divide promptly in a definite series of crops, some early and some late, until finally the number of binuclear cells has been reduced to normal (about 5 per cent). Schultz, Hall and Baker described this process as one of "cytoplasmic lag."

Mitotic figures have not been found in any bile ducts. Ponfick,<sup>31</sup> Meder,<sup>8</sup> von Meister,<sup>7</sup> MacCallum<sup>10</sup> (1902) and Schultz, Hall and Baker,<sup>16</sup> however, noted them in proliferating bile ducts.

An interesting question concerns the extent of participation of bile ducts in the regeneration of hepatic cells. Maichand,<sup>17</sup> Ribbert<sup>18</sup> and Muir<sup>12</sup> denied the proliferation of bile ducts in human beings, and attributed the apparent proliferation to either degeneration or regeneration and rearrangement of the hepatic cells in an effort to preserve their continuity. On the other hand, Meder,<sup>8</sup> Canalis,<sup>19</sup> Stroebe,<sup>20</sup> Barbacci,<sup>9</sup> MacCallum,<sup>10</sup> Hess,<sup>14</sup> Hess,<sup>23</sup> Miller and Rutherford<sup>22</sup> and Herxheimer and Gailach<sup>15</sup> all believed that bile ducts proliferate and, excepting Canalis,<sup>19</sup> believed that these proliferating ducts served as a source for the growth of new hepatic cells, at least under conditions of stress. They found the first evidence of regenerative activity in the proliferating bile ducts. Most textbooks agree on this point.

As regards the proliferation of bile ducts induced experimentally, Milne<sup>13</sup> alone denied that it was constant and asserted that its occurrence was adventitious. Von Podwyssozki,<sup>6</sup> Ponfick,<sup>31</sup> von Meister,<sup>7</sup> Flock<sup>42</sup> Poicile,<sup>48</sup> Hayami,<sup>49</sup> Schultz, Hall and Baker<sup>16</sup> and Bell<sup>54</sup> believed that bile ducts proliferate and all except Ponfick, von Meister and Flock gave to the budding bile ducts a definite part in the regeneration of hepatic cells. Whipple and Sperry<sup>32</sup> found proliferation of bile ducts only when they cut wedges from the surface of the liver and not from prolonged chloroform anesthesia by itself. Herxheimer and Gailach,<sup>15</sup> with serial sections, showed all the gradations from the typical bile duct, through the zone of proliferation and transitional cells, to the newly formed hepatic cells.

The consensus of opinion is that bile ducts proliferate and serve as a source of new hepatic cells, especially when the destruction of parenchyma has been severe. Since 70 per cent of the liver was removed

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60 Milne (footnote 13) Miller and Rutherford (footnote 22)

in these experiments, the remaining portion might revert to any available source of aid in regeneration. This conclusion is warranted by the appearance of large numbers of buds of the bile ducts on the sixth day, which persisted until the seventh or eighth week.

The lobules of the liver do not hypertrophy during regeneration. Comparatively low-power photomicrographs of sections removed at varying intervals did not reveal variation from normal. Although Ponfick,<sup>31</sup> von Meister<sup>7</sup> and Flock<sup>42</sup> believed that lobules hypertrophied, Mall<sup>43</sup> showed clearly that the process was not one of hypertrophy but rather of the formation of new complex lobules, and that the so-called clove-leaf-shape and heart-shape lobules represented an old lobule surrounded by newly formed lobular buds. This budding was extremely rapid, and the profusion of new hepatic cells, combined with the irregularity of the lobules, makes the picture confusing.

Mitotic figures are more numerous in the peripheral zones than elsewhere in the lobules. Ponfick<sup>31</sup> and von Meister<sup>7</sup> noted this and regarded it as further indication of lobular hypertrophy. The peripheral zone is the region of proliferating bile ducts, transitional cells and recently divided hepatic cells, the site where new lobules are forming. It is impossible to distinguish new lobules from old lobules, since both are penetrated by proliferating bile ducts. In short, the regenerating liver presents a picture of uniform, although irregular, lobules with growth most active at their peripheries in the region of the budding bile ducts.

The ability of the liver to regenerate is potentially infinite. Von Meister<sup>7</sup> first made this observation. The liver continues to restore itself after partial hepatectomy for the second or even the third time exactly as it does after the first. Technical difficulties concerning hemostasis impose limitations on carrying this process forward indefinitely. When the liver has been pared down to one greatly hypertrophied lobe, further resection is impossible since the capsule of Glisson is much too friable to hold any sort of hemostatic suture.

#### SUMMARY

When from one fifth to three quarters of the liver has been removed from a dog, the remaining part regenerates completely in from six to eight weeks. The process consists of marked hypertrophy of the remaining lobes. The pedicle does not regenerate. Restoration takes place within remaining lobes which hypertrophy until they attain at least four fifths of the size and weight of the original liver.

Extreme congestion of the sinusoids is the earliest change in the liver. The cells become swollen and pale. Mitotic figures appear in the peripheral zones of the lobules as early as the second day after partial hepatectomy, but are most numerous from the third to the sixth day.

Many binuclear cells are present shortly after operation, but evidence of amitotic division, namely nuclear fission, is lacking. The so-called cytoplasmic lag is offered in explanation of this seeming contradiction. The nuclei divide promptly by mitosis, but the cytoplasm permits the lapse of varying periods of time before it separates into the daughter cells.

Regeneration closely resembles the embryonic development of the liver. The chief cellular activity is at the periphery of the lobules, where bile ducts send forth buds of proliferating cells. Although hepatic cells are the main source of new tissue, buds of the bile ducts seem to play a definite part in regeneration of the liver. The transition from these proliferating duct cells to new hepatic cells is very gradual. The stress of regeneration has caused reversion to the primitive mode of production of hepatic cells in which the undifferentiated capillaries of the bile ducts give rise to new hepatic cells by dichotomous branching.

The other elements of the liver, including the connective tissue, the sinusoidal endothelium and the lymphatic endothelium, are carried along on the wave of growth without appreciable delay.

There is a marked increase in the glycogen content of the liver, especially in the periportal zones, from the first to the fourth weeks after partial hepatectomy. Glycogen is contained in large vacuoles in the cytoplasm. The fat content of the liver increases for four days and then falls slowly until the normal content is again reached ten days later.

At the end of from six to eight weeks, sections reveal tissue indistinguishable from normal liver, with the possible exception that proliferating bile ducts rarely persist.

The lobules do not hypertrophy but undergo a hyperplastic, budding process at their periphery, productive of new lobules so similar in size and shape that they cannot be distinguished from the old ones. Here, again, the analogy to the embryologic development of the liver is evident.

The liver appears to possess an infinite capacity for regeneration. The remaining part of the liver responds as rapidly and completely after the second or third partial hepatectomy as after the first.

#### ILLUSTRATIVE PROTOCOL

A white and brown bull terrier, weighing 11.7 Kg, was operated on Jan 27, 1926, under ether anesthesia. The left lateral, left central and right central lobes of the liver were removed, weighing respectively 122, 56 and 92 Gm, or a total of 270 Gm, which was approximately 70 per cent of the original amount of tissue, estimated on this basis to be 386 Gm. Uneventful recovery followed.

Thirty-five days later, the animal (then weighing 11.6 Kg) was explored. A specimen of liver was removed from the caudate lobe, and was fixed in Zenker's fluid and a diluted solution of formaldehyde USP (1:10). The right lateral and caudate lobes, which remained, were markedly enlarged, their edges were rounded, and the lower border of the liver was well down below the costal margin on the right. The animal was in good condition.



On June 2, 1926, 126 days after the first operation, the animal, then weighing 13.5 Kg, was explored. The right lateral lobe, weighing 132 Gm, was removed. This was equivalent to 50 per cent of the total amount of liver at this time.

The animal was explored again 176 days after the first operation. The dog's weight was 12.8 Kg. The caudate lobe, now the only remaining one, showed marked hypertrophy. A wedge-shaped section was removed from the edge of the lobe.

On Feb. 16, 1927, 385 days after the first partial hepatectomy, the animal (then weighing 11.9 Kg) was killed under ether by bleeding. The caudate lobe appeared as two lobes due to the marked enlargement of the papillary projection of the caudate lobe. The liver weighed 570 Gm, and was macroscopically normal in color and consistence. Histologically, the section showed normal hepatic tissue. Lobular hypertrophy or bile duct proliferation could not be seen.

# MICROSCOPIC CHANGES OF MUSCLE IN MYOSTATIC CONTRACTURE CAUSED BY TETANUS TOXIN \*

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When an appropriate dose of tetanus toxin is injected into one limb of a highly resistant animal, such as the rabbit or the rat, only the muscles of the leg which receives the injection are affected. When this local tetanus is fully developed, the limb is held continuously in rigid extension. In the early stages, the limb relaxes when the animal is anesthetized, but in from five to seven days after the injection, if the dose has been an adequate one the muscles become set in this posture of rigid extension and fail to relax under deep anesthesia or even after section of the motor nerve (Meyer and Ransom,<sup>1</sup> Ranson and Morris<sup>2</sup>). By section of the nerve the muscles are put at rest, yet they remain shortened and are able to support considerable loads without being drawn out to their original lengths.

To this shortened state of resting muscle, we have applied the term myostatic contracture<sup>3</sup> to differentiate it from the hypertonic contractures, which are maintained by a continuous stream of nerve impulses into the affected muscles. Familiar examples of muscles that have acquired a shorter than normal resting length are furnished by the contractures that restrict the movements of joints after immobilization of the latter for weeks in plaster casts, the permanent shortening of muscles after the division of their tendons and in their early stages at least, the parietic contractures due to the unequal paralysis of antagonistic groups of muscles in anterior poliomyelitis and multiple neuritis.

It is not easy to understand why a muscle cut off from its innervation should remain shortened. A preliminary histologic study showed that the myostatic contracture of local tetanus was not due to fibrosis (Ranson and Sams<sup>3</sup>). It was thought that there might be an accumulation of lactic acid in the muscle in tetanus, and that the failure to

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1 Meyer, H, and Ransom, F. *Arch f exper Path u Pharmacol* **49** 369 1903

2 Ranson, S W and Morris A W. *J Comp Neurol* **42** 99, 1926

3 Ranson, S W, and Sams, C F. *J Neurol & Psychopath* **8** 304, 1928

relax might in this respect resemble the delayed relaxation of fatigued muscle. But an investigation of this question showed that the lactic acid content of muscles in the contracture of tetanus was not above normal.<sup>4</sup>

In the hope of gaining some further insight into the nature of the contracture, we undertook a detailed study of the histologic changes in the tetanic muscles. So far as we were able to learn, this had not been attempted before. Most investigators who had studied the pathology of tetanus had directed their attention to the changes in the nervous system, and those who had examined the muscles had been concerned either with local inflammatory reactions produced by the tetanus bacillus (Stangl<sup>5</sup>) or with muscles obtained at autopsies in fatal cases of general tetanus (Wisbaum<sup>6</sup>). Since, in general tetanus, myostatic contracture seldom develops, such material could contribute nothing to the solution of our problem.

Wisbaum studied sections of the psoas and the quadriceps obtained at autopsy in a case of general tetanus complicated by terminal pneumonia. Hemorrhagic areas were found among the muscle fibers. Within these areas were the remains of degenerating muscle fibers. Large mononuclear cells, rich in cytoplasm, with lightly staining nuclei, were scattered through the hemorrhagic areas. Nuclear proliferation was seen in some of the adjacent muscle fibers. These muscle nuclei bore a close resemblance to those of the mononuclear cells in the hemorrhagic areas. In cross-sections typical pictures of waxy degeneration could be seen. These changes were similar to those seen by Forbus<sup>7</sup> in the rectus abdominis after death from pneumonia. Hence, it is not clear what part if any of the alterations described by Wisbaum were due to the action of tetanus toxin.

#### METHOD

In our work, local tetanus was produced in rats by the injection of tetanus toxin into the muscles above the popliteal space of the right hind leg. The dose of toxin necessary to produce local tetanus had to be determined by experience with the particular strength of toxin used, since it is subject to some deterioration. When freshly prepared, the toxin, which was kindly furnished us by the Research Laboratory of Parke, Davis & Company, was standardized so that 0.001 cc constituted a minimum lethal dose for a guinea-pig. Even when fresh, 0.005 cc of this toxin was required to produce high grade local tetanus in rats weighing 150 Gm. As the toxin aged, this had to be increased up to 0.04 cc. Two days

4 Davenport, H. A., Davenport, H. K., and Ranson, S. W. *J. Biol. Chem.* **79**: 499, 1928.

5 Stangl, F. H. *J. Infect. Dis.* **31**: 22, 1922.

6 Wisbaum, K. *Deutsche Ztschr. f. Nervenhe.* **80**: 75, 1923.

7 Forbus, W. D. *Pathologic Changes in Voluntary Muscle: Degeneration and Regeneration of Rectus Abdominis in Pneumonia*, *Arch. Path.* **2**: 318 (Oct.) 1926.

after the injection of the toxin, the patellar tendon was cut to permit flexion of the knee and complete contraction of the gastrocnemius

The earliest stages of local tetanus in which myostatic contracture had developed were studied, the criterion for determining its presence being the failure of the muscle to relax under deep ether anesthesia. In six of the rats, contracture developed in five days from the time of injection, in the remainder, it required seven or eight days for the toxin to produce the permanent contracture desired.

In order to eliminate artefacts as much as possible, the method of removing and fixing the muscles was varied. It was found that the best preparations were obtained when the gastrocnemius muscle was dissected out immediately after the animal had been killed with ether, and suspended in a moist chamber under a tension of 25 or 50 Gm. for one hour before being placed in the fixing fluid with the weight still attached. This interval allowed between death and fixation prevented the twitching that usually takes place when a recently removed muscle is placed directly in fixative. Straight fibers were thus obtained. Three fixatives Bounin's solution, Zenker's fluid and a diluted solution of formaldehyde U. S. P. (1:10) were used in order that several stains might be employed. The stains were hematoxylin and eosin, iron hematoxylin, van Gieson's picrofuchsin with Delafield's hematoxylin, Mallory's triple connective tissue stain and Mallory's phosphotungstic hematoxylin.

Paraffin sections of the right (tetanic) and the left (control) gastrocnemii 8 microns thick were mounted on the same slide to insure uniformity of treatment. Although in rats with tetanus the muscles in which no injections were made appeared little altered, it was thought best to use the gastrocnemii of normal animals for controls, as well.

It was found that Mallory's triple stain gave the best definition of striation, as well as differentiation of connective tissue. Hematoxylin-eosin and van Gieson's stain showed nuclear and degenerative changes most clearly. Iron hematoxylin and phosphotungstic hematoxylin were used more for checks on changes noted with the other stains.

Longitudinal sections and cross-sections were examined for changes in the staining of the tetanic muscles with the different dyes, for nuclear changes, for difference in diameter between fibers of the tetanic muscles and those of the control side of the same animal, for degenerative changes and for changes in the striations. Enlarged photomicrographs of cross-sections of the tetanic and of the control muscles were used for measuring the diameters of the fibers. The fibers of four areas on the tetanic side and four comparable areas on the control side were measured. Two measurements, one through the greatest and one through the smallest diameter, were made of each fiber and an average of these taken as the approximate diameter of the fiber. The striations were measured directly with the use of a filar micrometer and the oil immersion objective. In a given portion of a fiber, consecutive isotropic and anisotropic bands were measured for as great a distance as the stripes remained parallel. Such measurements were made on tetanic and control muscles of the same rats and on muscles of normal rats. Table 2 shows only averages of such consecutive measurements in given areas.

In six of the experiments, the muscles were measured after fixation in a diluted solution of formaldehyde U. S. P. (1:10) under a tension of 25 Gm. The length of the muscle and the length of a definite, easily identifiable bundle of parallel fibers was determined.

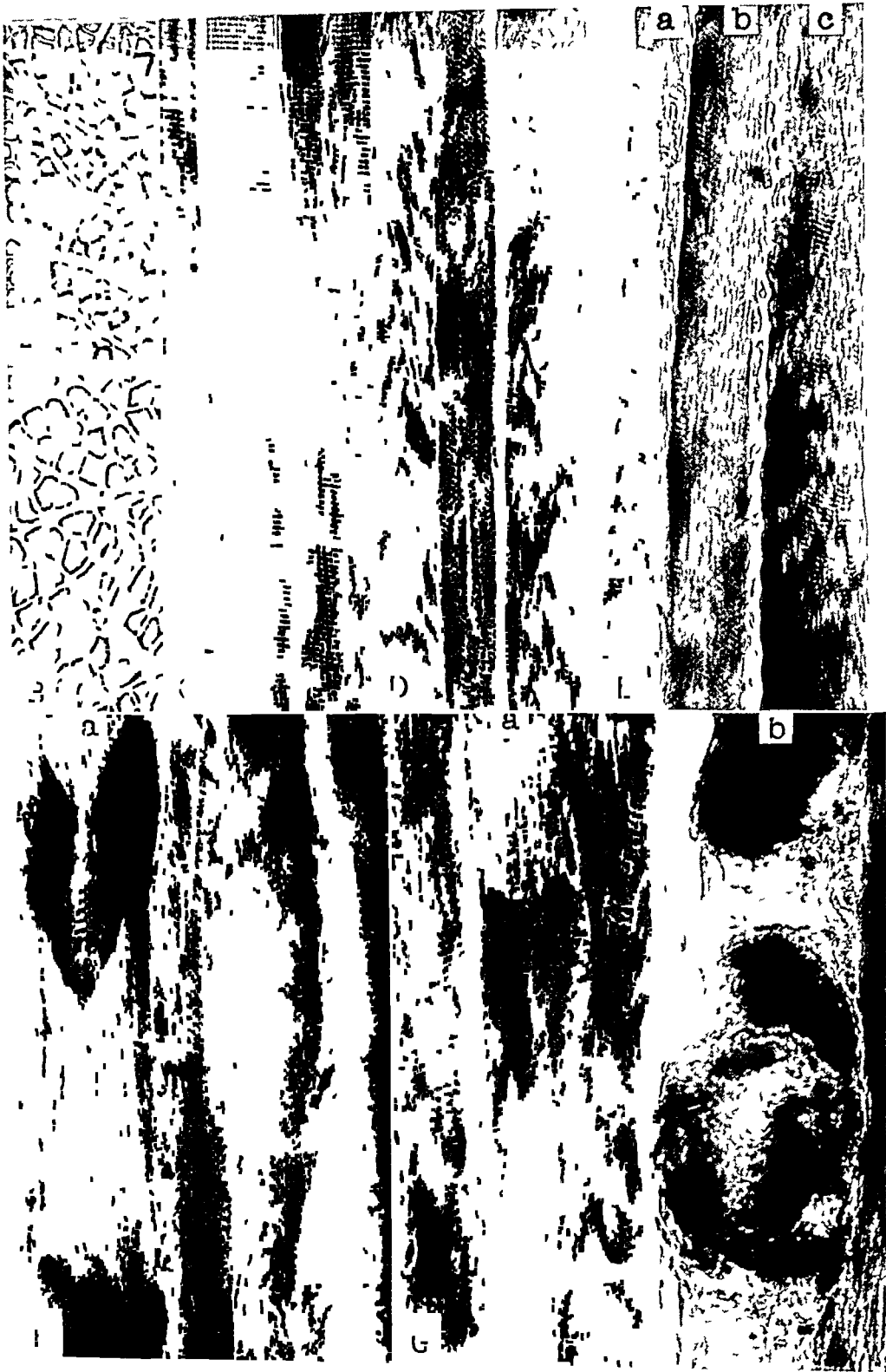


Figure 1

## EXPLANATION OF FIGURE 1

Fig 1—*A* represents a transverse section of the medial head of the left (control) gastrocnemius of rat T-XXVII,  $\times 100$  *B* represents a transverse section of the medial head of the right (tetanic) gastrocnemius of rat T-XXVII,  $\times 100$  The portions illustrated in *A* and in *B* were taken from corresponding areas of the two muscles *C*, a longitudinal section of normal muscle (gastrocnemius, rat N-XIX) Mallory's triple stain after Bouin fixation,  $\times 285$  *D*, a longitudinal section of tetanic muscle (gastrocnemius, rat T-XXVIII) showing mottled staining in two fibers and blurred striations without irregular staining in the center fiber Mallory's triple stain after Bouin fixation,  $\times 285$  *E*, a longitudinal section of tetanic muscle (gastrocnemius, rat T-XXVIII) Fibers *a* and *c* show mottled staining with striations pulled out of alignment to some extent Fiber *b* shows blurring of the cross striations without irregularity in staining In such a fiber the myofibrils have been pulled out of alignment to such a degree that the striations are continuous across only small groups of fibrils Mallory's triple stain after Bouin fixation,  $\times 285$  *F*, a longitudinal section of tetanic muscle (gastrocnemius, rat T-XXVII) Fiber *a* shows darkly staining areas with a light stretched area between In such stretched areas, the isotropic bands are wider and the *I/Q* ratio increased Striations can be seen in parts of the dark areas, but they are not distinct enough to measure Mallory's triple stain after Bouin fixation,  $\times 400$  *G*, a longitudinal section of tetanic muscle (gastrocnemius, rat T-XXVII) Fiber *a* is similar to *a* in figure 1 *F* Fiber *b* shows a darkly stained granular area with light regions, which also appear to be disintegrating, on each side of it It seems probable that this represents a later stage in the same process of alteration that is taking place in figure 1 *F*, *a* and in fiber *a* of this figure Mallory's triple stain after Bouin fixation,  $\times 400$



Figure 2

## EXPLANATION OF FIGURE 2

Fig 2—*A* represents a longitudinal section of normal muscle (gastrocnemius, rat N-XIX) showing the orderly arrangement of muscle nuclei with their long axes parallel to the long axes of the fibers. Hematoxylin and eosin,  $\times 145$ . *B*, a longitudinal section of tetanic muscle (gastrocnemius, rat T-XXVII) eight days after the injection of toxin, showing an aggregation of nuclei within fiber *a*. Note that the fiber is continuous with the nucleated area at each end. The two fibers above *a* show some increase in the number of muscle nuclei. The nuclei of most of the fibers illustrated here do not have the normal arrangement with reference to the long axes of the fibers. Hematoxylin and eosin,  $\times 145$ . *C*, a longitudinal section of tetanic muscle (gastrocnemius, rat T-XVII) seven days after the injection of toxin. The animal died of general tetanus at this time. Fiber *a* shows a granular area with an increase in the number of nuclei around the edges of it. *b*, *c* and *d* are fibers with pronounced longitudinal striation. Here also may be seen the marked dark and light staining and an apparent loss rather than increase in the number of nuclei in parts of the fibers. Hematoxylin and eosin,  $\times 145$ .



retains its normal relation to Krause's membrane Nageotte<sup>8</sup> obtained a similar picture from muscles in which contracture had been produced by electrical stimulation He interpreted this mottled appearance as a contraction of the fiber in spots, for the areas between the dark areas showed striations at the usual normal spacings He believed that in the parts of the dark fields where striations could not be seen, the dark disks had drawn so close together that the space between them became invisible, since very fine striation was present in the dark areas if the muscle had been pulled out slightly before being fixed With contracture due to chloroform, he<sup>9</sup> obtained histologic pictures that corresponded to various stages of faradic contraction In early contraction due to chloroform, the contracted areas were small and finely striated, in later stages, they were larger and more like the extreme faradic contracture

That the change in staining reaction observed in longitudinal sections was not merely on the surface of the fibers was shown by transverse sections Here one might see fibers that were spotted with light and dark areas A transverse section through almost any plane in fiber *a*, figure 1 *E*, would be expected to show spotted staining On the other hand, fiber *b* in figure 1 *E* should show a cross-section practically uniform in color A transverse section through the light part of *a* in figure 1 *F* would be lighter than normal, though probably uniform in color, while one through either of the wide dark areas of the same fiber should be uniform also, but darker than normal In almost any single cross-section of tetanic muscle all of these variations could be seen

In our preparations, a measurement of isotropic and anisotropic bands in the dark and light areas in different stages of development, indicated that mottling may appear before the relationship between the widths of the isotropic and anisotropic disks and the sarcomere length changes, for in some fibers, such relationships were found to be the same as those found in normal muscle In later stages, however, the relationships were altered Measurements were made in six normal muscles, and it was found that the sarcomeres varied in length from 2.5 to 2.9 microns, the *J* disk from 1.26 to 1.5 microns, the *Q* disk from 1.27 to 1.46 microns and the *J/Q* ratio from 0.86 to 1.03 The muscles in the contracture of tetanus did not show any considerable variation in the *J/Q* ratio except in the stretched light areas, where this ratio was greatly increased, and possibly in the dark adjacent areas, which could not be measured

As can be seen from figure 1 *D*, *E*, *F* and *G*, the contracture of tetanus did not present a uniform picture The great distortion of the fibrils in many of the fibers prevented the measurement of the striations.

8 Nageotte, J. *Compt rend Acad d sc* **180** 761, 1925

9 Nageotte (footnote 8, p 1963)

transverse striations The ground membranes of Krause, designated by the letter *Z*, are supposed to extend across the fiber binding the fibrils together If this is the case the interfibrillar portions of these membranes must be dissolved or disrupted in some of the fibers in the contracture of tetanus At any rate, it is certain that in such fibers the individual myofibrils separate from one another and are more easily seen than in normal muscle Instead of being straight and parallel to the long axis of the fiber, they are bent on themselves, giving the fiber an irregular but rather pronounced longitudinal fibrillation (as may be seen in fiber *d* in fig 2 *C* and in fiber *a* in fig 1 *E*) As a result of these changes, the dark disks in adjacent fibrils lose their exact transverse alignment and the striations become obscured (as in *b* in fig 1 *E*)

*Changes in Staining*—The most striking histologic change found in all specimens of tetanic muscle was an irregular mottling of the fibers, in which there appeared dark and light staining areas of irregular contour, varying considerably in width In some instances, the anisotropic elements seemed to have lost their staining property, producing the irregular light fields, while some areas of the fiber retained it, giving the dark fields (fig 1, *D* and *E*) In others, the dark areas stained darker than normal, while the light areas seemed to have lost either in part or entirely the staining property of the anisotropic bands (*Q*), the *z* line remaining faintly visible In some of the cases in which the dark areas were darker than the normal staining of a fiber, the *Q* bands appeared to be crowded close together, almost obscuring the isotropic bands In others, there was normal spacing, so that the dark staining here could not be accounted for by approximation of anisotropic bands Parts of some of these extremely dark areas appeared homogeneous, with the striations distinguishable only where they joined the light ones In fibers so stained, the light areas between dark ones appeared to have been stretched (as in *a* in fig 1, *F* and *G*)

Irregular staining was shown with all the dyes used It was a matter of dark and light shading of the same color in sections stained with hematoxylin and eosin, picrofuchsin, Mallory's triple stain after formaldehyde or Bouin fixation and phosphotungstic hematoxylin In sections stained with iron hematoxylin, the light areas appeared unstained or lightly stained, while the dark ones were dark blue or black

Mallory's triple stain after Zenker fixation stained the anisotropic bands of the normal muscle blue and the isotropic bands orange, the *z* line appearing brown In tetanic muscle, the same areas that stained light with other stains were orange and the dark areas were blue The *Q* bands remained visible as brown stripes in the orange fields after they no longer stained blue This would indicate that although the anisotropic disk may change in its staining reaction, it

seen in many of the dark regions, they were greatly distorted, or the definition was poor owing to the deep staining. It could not be determined by measurement therefore, whether or not a shortening of sarcomeres had taken place in the dark regions which was proportional to the amount that they were shown to have lengthened in the lightly stained areas.

According to one theory (Jordan<sup>10</sup>), contraction in striped muscles is associated with a genuine reversal of striations as regards the deeply staining substance of the *Q* bands. These dark bands split into two halves, which separate and approach the *z* membranes that limit the sarcomeres at either end. In this way, contraction bands are formed, each of which is composed of the fused opposite halves of two adjacent *Q* bands. We have not been able to find any evidence of such contraction bands in our preparations of the tetanic muscle. Certainly, the dark areas that sometimes stretched bandlike across a fiber (as in *a* of fig 1 *F*) were not contraction bands in this sense, since they were much too wide, and since, under favorable conditions, transverse striations could be seen in them.

Measurements of striations in the control muscles of the same animals showed only normal variation.

*Degenerative Changes*—Two types of degeneration were observed. One appeared to follow the extreme light and dark banding in which portions of the fiber were stretched (as in fig 1 *F* fiber *a*). Here the dark portions became granular and the light parts disintegrated (as in fig 1 *G* fiber *b* and fig 2 *C* fiber *a*). There sometimes was and sometimes was not an aggregation of nuclei about these granular areas, but when there was, most of them were found in the light regions at the edges of the dark granular areas. In the stage preceding granulation of the deeply staining parts of the fiber (fig 2 *C* fibers *b*, *c* and *d*), muscle nuclei seemed to be even less numerous than in normal muscle. This type of degeneration was not seen in animals earlier than seven days after injection of the toxin. The other type of degeneration was found in muscles that reached the state of permanent contracture as early as five days from the time of injection, as well as in later stages, but it never involved more than a small percentage of the fibers. This degeneration was characterized by an aggregation of a large number of nuclei within a fiber, some of which appeared to be muscle nuclei in greater numbers than normal, and some, large mononuclear cells. Such an aggregation may be found throughout the greater part of a single fiber or only in a small portion of a fiber, as shown in *a* in figure 2 *B*. Serial sections of such a fiber showed that the nuclei were within the fiber and not merely on the surface. In some places, the muscle fiber

10 Jordan, H. E. *Am J Anat* 27 1, 1920

Many of the measurements made in less distorted areas did not show any variation from the normal. Such measurements as it was possible to make in fibers showing different degrees of irregular staining showed variations ranging from normal relationships of isotropic and anisotropic bands in both light and dark staining areas, to a narrowing of the isotropic bands and consequent shortening of the sarcomere in the dark areas, and either a normal sarcomere length and  $J/Q$  ratio, or a lengthened sarcomere resulting from an increase in the width of the isotropic bands in the light areas. All these variations have been recorded in table 2, in which an example of the average widths of the  $Q$  and  $J$  disks in adjacent light and dark staining areas of the same fiber has been taken from each of four different animals. In rat T-XXII, the lengths of the sarcomeres and the  $J/Q$  ratios in both

TABLE 2—Average Widths of Isotropic and Anisotropic Disks in Comparable Areas of Irregularly Staining Fibers in Tetanic Muscles from Four Different Animals

Rat*	Type of Area	Sarcomere (Microns)	J Disk (Microns)	Q Disk (Microns)	J/Q Ratio
T-XXII	Dark	2.6	1.15	1.40	0.82
	Light	2.5	1.22	1.30	0.94
T-XXIII	Dark	2.4	1.10	1.35	0.81
	Light	2.3	1.05	1.27	0.83
T-XXVIII	Dark	2.2	0.91	1.31	0.69
	Light	2.6	1.32	1.30	1.01
T-XVII	Stretched (light)	3.7	2.37	1.30	1.82
	Stretched (light)	3.6	2.20	1.28	1.72
	Stretched (light)	3.3	2.00	1.26	1.59
T-XXVIII	Stretched (light)	3.2	1.82	1.34	1.36

\* In the first three animals listed, the light and dark staining areas were adjacent and in the same fiber. The dark areas adjacent to stretched light areas could not be measured, so that for these there are no corresponding measurements in dark areas.

the light and the dark areas of the same fiber were within the range of values found in normal muscle. Rat T-XXIII showed somewhat shortened sarcomeres and a slightly lowered  $J/Q$  ratio in both the light and the dark areas. Rat T-XXVIII, however, showed a difference in the relationships of the widths of the  $J$  and  $Q$  disks as between the dark and the light areas as follows. The sarcomeres of the dark field were shortened as a result of the narrowing of the  $J$  disks, the  $Q$  disks remaining normal in width. The adjacent light area, however, showed normal sarcomere lengths and normal  $J/Q$  ratio. The stretched light areas of the muscle in rat T-XVII and rat T-XXVIII showed marked increase in sarcomere length and in the width of the  $J$  disk. Here, also, the  $Q$  disk retained its normal width, so that it seemed from these figures that the variations occurred in the  $J$  disks rather than in the  $Q$  disks. In those fibers in which the light areas were stretched and the dark ones were unusually compact, it was not possible to measure the striations in the dark ones. Though striations could be

No increase in either intrafascicular or interfascicular connective tissue was found in any of the preparations

Vacuoles were observed in muscles five, seven and eight days after the injection of the toxin, though not all specimens showed them. These were best seen in cross-sections, but if there was a greater degree of vacuolation, they were apparent in longitudinal sections also, the fibrils being widely separated in parts of the fiber. In a number of fibers in which we noted vacuolation in cross-sections, we saw nuclei in the interior of the fiber near the edges of the vacuoles. Auriat<sup>12</sup> described fibers with widely separated fibrils having clear spaces between them in preparations of muscles in which experimental edema had been produced. The vacuoles in our preparations presented such an appearance, though in the gross the muscles did not seem edematous. When the toxin of tetanus was injected into the muscles on the back of the thigh, little edema of the leg was seen even in advanced local tetanus. To determine the extent of edema in the muscles, the right and the left gastrocnemii of five rats with the contracture of tetanus were weighed after fixation in a diluted solution of formaldehyde U.S.P. (1:10) and placed in a desiccator. They were again weighed after five days, seven days and two weeks of drying. Both the tetanic and the control muscles lost water at the same rate, and the final weighing showed that the tetanic muscles had been reduced to 19.8 per cent and the control muscles to 20.3 per cent of their original weight. This difference of 0.5 per cent between the dry weights of the muscles of the two sides seems insignificant to us.

The changes found in the gastrocnemius muscle were present to an even more marked extent in the soleus muscle.

#### SUMMARY

In advanced stages of local tetanus, the extensor muscles fail to relax after section of the motor nerves. This myostatic contracture was studied histologically in the gastrocnemius and soleus muscles of white rats. There is no increase in connective tissue and the contracture is not due to fibrosis. The muscle fibers undergo changes, but what relation these changes bear to the shortening of the muscle is not obvious.

The muscle fibers show a blurring of the cross striations and a mottled staining. The blurring of the cross striations appears to be due, in part, to a disruption of whatever holds the myofibrils in close juxtaposition and accurate transverse alignment. The fibers acquire a wavy longitudinal striation due to the greater evidence of the individual fibrils. The mottling is due to changes in staining reaction of different

<sup>12</sup> Auriat, G. *Compt. rend. Soc. de biol.* **97** 73, 1927

seemed to have been entirely replaced by such nuclei, which filled the tube formed by the sarcolemma. Wisbaum<sup>6</sup> noted a similar degeneration of single fibers in specimens of tetanic muscles. In such fibers, he observed an increase in the number of muscle nuclei, which in the process of degeneration were only slightly different in appearance from large mononuclear cells which he had seen in hemorrhagic areas between fibers. Stangl<sup>5</sup> injected a suspension of tetanus bacilli into the thighs of guinea-pigs. In the earlier stages, within twelve hours after the injection, there was a local reaction defined by cellular invasion in which polymorphonuclear leukocytes predominated. A few mononuclear leukocytes and large mononuclear wandering cells were also present. The nuclei of the sarcolemma were swollen. Five or six days later, waxy degeneration, disappearance of striations and disintegration of nuclei were seen in muscle fibers in the immediate vicinity of the proliferating tetanus bacilli. Forbus<sup>7</sup> described waxy degeneration in scattered fibers of the rectus abdominis muscles in patients suffering from pneumonia. A swelling of the fiber was followed by proliferation of muscle nuclei, loss of striation and disintegration of the contractile substance. The fiber was then invaded by large mononuclear phagocytic cells. These changes sometimes occurred in single fibers or even in parts of fibers. They were observed in cases of only four days' duration of the disease. In experimentally produced degeneration, he<sup>11</sup> demonstrated by vital staining that the phagocytic cells originated outside the fiber. Although the aggregations of nuclei that we have observed in a few fibers in tetanus appeared similar to those which he described, we did not observe the swelling of individual fibers preceding such an increase in the number of nuclei.

While an increase in the number of muscle nuclei was apparent in many fibers of tetanic muscle, still, regions could be found where an increase could not be seen, as shown in portions of figure 2 C. This might have been expected, since the other effects of the toxin were not uniform throughout the muscle. Two kinds of nuclei were observed in the fibers of both normal and tetanic muscles, a long, oval type and a large, rounded type, both staining lightly with hematoxylin. Where an increase in number was noted, it concerned both kinds, the long oval nuclei frequently being found in chains of from three to five or more, or in groups closely packed together, the round ones in groups of from five to seven, but with the individual nuclei slightly separated from one another. Fragmented nuclei were also sometimes seen, especially in regions in which degeneration was more advanced. Nuclei of the oval type seemed slightly swollen in the tetanic muscles.

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11 Forbus (footnote 7, p. 486)

# A HISTOLOGIC STUDY OF THE FORMATION OF BILE PIGMENT \*

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The purpose of this report is to present histologic evidence bearing on the origin and on the site of the formation of bile pigment. An endeavor has been made to demonstrate in the various tissues of the body the splitting up of hemoglobin into bile pigment and free iron. Recent articles by Mann,<sup>1</sup> Rich,<sup>2</sup> M'Nee,<sup>3</sup> and Whipple<sup>4</sup> are excellent reviews on this subject. Aschoff,<sup>5</sup> Oberling,<sup>6</sup> and Krumbhaar<sup>7</sup> have summarized present views concerning the reticulo-endothelial system.

One of the first observations of the extrahepatic formation of bile pigment was made by Virchow<sup>8</sup> in 1847. He found a substance which he called hematoidin occurring in the tissues around old hemorrhages discovered at necropsy. The hematoidin, which occurs both intracellularly and lying free in the tissues, is identical in all its physical and chemical properties with bilirubin, as has been shown recently by Rich and Bumstead.<sup>9</sup> Hooper and Whipple<sup>10</sup> discovered bilirubin on the day following the introduction of a solution of hemoglobin into the

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<sup>1</sup> From the Division of Experimental Surgery and Pathology, The Mayo Foundation

1 Mann, F C The Site of Formation and Source of Bilirubin, Arch Path **2** 516 (Oct) 1926

2 Rich, A R The Formation of Bile Pigment, Physiol Rev **5** 182, 1925.

3 M'Nee, J W Jaundice, a Review of Recent Work, Quart J Med. **16** 390, 1922-1923

4 Whipple, G H The Origin and Significance of the Constituents of the Bile, Physiol Rev **2** 440, 1922

5 Aschoff, Ludwig Lectures on Pathology, New York, Paul B Hoeber, 1924

6 Oberling, C Le systeme reticulo-endothelial, Ann d'anat path **1** 87, 1924

7 Krumbhaar, E B The So-Called Reticulo-Endothelial System, Its Relation to Phagocytosis Defense Processes, Lipoid and Protein Metabolism, Destruction of Red Cells and to Neoplasms, Internat Clin **2** 280 (35th s) 1925

8 Virchow, R Die pathologischen Pigment, Virchows Arch f path Anat **1** 379, 1847

9 Rich, A R, and Bumstead, J H On the Identity of Haematoidin and Bilirubin Bull Johns Hopkins Hosp **36** 225, 1925

10 Hooper, C W, and Whipple, G H Icterus A Rapid Change of Hemoglobin to Bile Pigment in the Pleural and Peritoneal Cavities, J Exper Med **23** 137, 1916

parts of the same fiber, some areas staining more heavily, others more lightly than normal

In some instances the lightly stained areas represent stretched portions of the muscle fibers. Here the ratio of the widths of the *J* bands to the *Q* bands is high, owing to the widening of the *J* bands. In other areas, the ratio is normal, and in some it appears to be slightly reduced as a result of the narrowing of the *J* bands.

A small percentage of the muscle fibers undergo degeneration. Where the separation into light and dark areas has been pronounced, the light fields may disintegrate while the dark ones become granular. A few other fibers become replaced either for short distances or throughout their lengths by nuclei, which fill the old sarcolemma. These appear to be derived, in part, from the nuclei of the muscle and, in part, from mononuclear cells that have invaded the fibers from without.



of hepatectomized geese following the administration of arseniuretted hydrogen M'Nee observed, in histologic studies of the normal goose's liver, that the Kupffer cells contained erythrocytes and gave a marked iron reaction In the livers of jaundiced geese, the Kupffer cells were seen to contain, besides many erythrocytes, large quantities of yellowish-green pigment, which resembled biliverdin, although chemical proof was lacking McNee concluded that, in geese, bile pigment was formed by the endothelial (Kupffer) cells of the liver and by the small number of endothelial cells found elsewhere (spleen and bone-marrow) In geese, hepatectomy accomplishes the removal of the greater part of the reticulo-endothelial system, but in mammals it does not

Before reviewing further experimental work, one should consider the type of cell of which the Kupffer cell is an example During the last half century, certain fixed cells and certain wandering cells having phagocytic properties have been studied by many workers Ranvier<sup>17</sup> gave the name "clasmatocytes" to phagocytic cells found in the connective tissues Mechnikov<sup>18</sup> divided phagocytes into two classes microphages or polymorphonuclear leukocytes and fixed tissue macrophages, which included the large cells of the splenic pulp and lymph nodes, the Kupffer cells of the liver, the neuroglia and nerve cells and certain cells of the connective tissues Ribbert,<sup>19</sup> in 1904, showed the interrelation of all these different cells in their common ability to engulf particles of lithium carmine injected into the circulation The marked phagocytic activity of the stellate (Kupffer) cells for particulate matter was demonstrated in a recent paper by Higgins and Murphy<sup>20</sup>

To Aschoff belongs the credit for the conception that these reticular and endothelial cells of the various tissues possess common properties and functions, and may be designated all together as the reticulo-endothelial system He divided the cells of this system into two groups reticulo-endothelial cells and histiocytes In the first group, he included reticular cells of the spleen, bone-marrow and lymphatic tissue, and endothelial cells of the liver, lymph sinuses, splenic sinuses, bone-marrow, suprarenal capillaries and hypophyseal capillaries To the second group, he assigned tissue histiocytes (clasmatocytes), splenocytes and blood histiocytes (endothelial leukocytes)

Many attempts have been made to determine what tissues are most active in the conversion of hemoglobin into bile pigment The forma-

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17 Ranvier, L Des clasmatocytes, *Arch d'anat micr* **3** 122, 1900

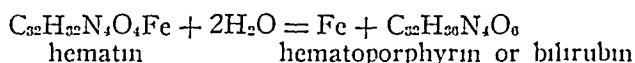
18 Mechnikov, E Immunity in Infective Diseases, Cambridge, Harvard University Press, 1905

19 Ribbert, Hugo Die Abscheidung intravenos injizierten gelosten Karmins in den Geweben, *Ztschr f allg Physiol* **4** 201, 1904

20 Higgins, G M, and Murphy, G T The Phagocytic Cells (v Kupffer) in the Liver of Common Laboratory Animals, *Anat Rec* **40** 15, 1928

pleural and peritoneal cavities of dogs Van den Bergh,<sup>11</sup> using his quantitative method, demonstrated a high content of bilirubin in old hematomas The conversion of hemoglobin into bile pigment in subdural hematomas was discussed recently by Putnam and Cushing<sup>12</sup>

That hemoglobin is one source, if not the only source, of bilirubin is indicated by a consideration of the probable formulas of these substances, and of the intermediary products The generally accepted view (Mathews<sup>13</sup>) is that hemoglobin splits up into a hematin and a globin fraction The hematin liberates iron and becomes hematopoiphyrin, which is isomeric with bilirubin, the reaction being represented by the equation



Biliverdin is formed by the oxidation of bilirubin The excessive formation of bilirubin, as shown by jaundice and bilirubinuria, in clinical conditions involving the massive destruction of blood gives further evidence in favor of the derivation of bilirubin from hemoglobin Such conditions include hemolytic icterus, pernicious anemia and paroxysmal hemoglobinuria

The problem with which this paper is chiefly concerned is that of the site of the formation of bilirubin As early as 1769, Morgagni<sup>14</sup> taught that the liver excreted the bile which was brought to it, preformed, by the blood An altogether different view was generally accepted for many years following the experiments of Minkowski and Naunyn,<sup>15</sup> in 1886, who found that jaundice was produced in geese by poisoning with arseniuretted hydrogen, whereas jaundice could not be so produced if the liver was removed immediately after the administration of this substance From this they concluded that the liver was necessary for the production of jaundice, and the belief arose that bile pigment was formed by the hepatic cell

The aforementioned experiments were repeated by M'Nee,<sup>16</sup> who found that small traces of bile appeared in the urine and the tissues

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11 Van den Bergh, A A H Der Gallenfarbstoff im Blut, Leiden, Van Doesburgh, 1918

12 Putnam, T J, and Cushing, Harvey Chronic Subdural Hematoma, Its Pathology, Its Relation to Pachymeningitis Hemorrhagica and Its Surgical Treatment, Arch Surg **11** 329 (Sept) 1925

13 Mathews, A P Physiological Chemistry, ed 4, New York, William Wood & Company, 1925

14 Morgagni, quoted by Rich (footnote 2)

15 Minkowski, O, and Naunyn, B Beitrage zur Pathologie der Leber und des Icterus Ueber den Icterus durch Polycholie und die Vorgange in der Leber bei demselben, Arch f exper Path u Pharmakol **21** 1, 1886

16 M'Nee, J W Experiments on Haemolytic Icterus, J Path & Bact **18** 325, 1913-1914

A new operative method which made it possible for dogs to survive total hepatectomy for several hours was devised by Mann and Magath<sup>29</sup> The operation was performed in three stages (1) production of a reverse Eck fistula, (2) ligation of the portal vein and (3) complete removal of the liver together with a segment of the inferior vena cava The animals were kept alive for from fifteen to thirty hours by the intravenous injection of a solution of dextrose Bile pigment appeared in the blood within from three to six hours after the hepatectomy, and its appearance could be hastened by the intravenous injection of hemoglobin Even the removal of all abdominal viscera failed to prevent the formation of bilirubin

Rich<sup>30</sup> noted striking results in the application of the method of tissue culture to this problem He added fresh erythrocytes to coverglass cultures containing wandering phagocytes of mesodermal origin These phagocytes were seen to ingest large numbers of erythrocytes, and as the hemoglobin of the latter was broken down, crystals of bilirubin and biliverdin appeared within the phagocytes The identity of these pigments was established by the microscopic Gmelin test and by their structure and color The Berlin blue reaction often demonstrated an iron-containing residue in these phagocytes by the side of the bile pigment

A few instances have been reported of the conversion of hemoglobin into bilirubin in the test tube, when such agents as trypsin and dextrose or pyogenic bacteria were employed Careful repetition of these experiments by Rich and Bumstead<sup>31</sup> failed to show the presence of bilirubin by the van den Bergh test and by extraction with chloroform

Since the results reported in this paper depend largely on the occurrence of inorganic iron in certain tissues, it seems advisable to summarize briefly the knowledge of the metabolism and distribution of iron in the body Asher<sup>32</sup> believed that the spleen stands first among the regulators of iron metabolism If this organ is removed, the excretion of iron through the intestines is increased, and anemia may result, unless this is prevented by the compensatory functioning of other

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29 Mann, F C, and Magath, T B The Effect of Total Removal of the Liver, *Tr Sect Path and Physiol, A M A*, 1921, p 29

30 Rich, A R The Formation of Bile Pigment from Haemoglobin in Tissue Cultures, *Bull Johns Hopkins Hosp* **35** 415, 1924

31 Rich, A R, and Bumstead, J H On the Alleged Power of Bacteria to Form Bile Pigment from Haemoglobin, *Bull Johns Hopkins Hosp* **36** 376, 1925, On the Question of the Formation of Bile Pigment from Haemoglobin by the Action on Enzymes, *Bull Johns Hopkins Hosp* **36** 437, 1925

32 Asher, Leon Ueber die Bedingungen der Blutbindung und des Eisenstoffwechsels, *Med Klin* **21** 1909, 1925

tion of bilirubin in the spleen has been proved by measurements of the bilirubin content of the splenic vein and artery. Van den Bergh and Snapper<sup>21</sup> reported that in five of six cases of hemolytic anemia the blood of the splenic vein contained more bilirubin than did that of the peripheral veins. Similarly, Rich and Rienhoff<sup>22</sup> found an increased amount of bilirubin in the blood of the splenic vein compared with that of the splenic artery and the peripheral veins in four of ten cases representing various pathologic conditions. In these two studies, the quantitative estimation of the bilirubin was made with the van den Bergh method. The spectrophotometric determination of the bilirubin content of the blood in vessels issuing from the spleen and from the bone-marrow showed, in the work of Mann, Bollman, Sheard and Baldes,<sup>23</sup> that more bilirubin was normally present in these vessels than in the arteries to the spleen and the bone-marrow. From a continuation of these studies with removal of the spleen or the liver or all abdominal viscera, they<sup>24</sup> concluded "While bilirubin is made in both the spleen and the liver the amount is insignificant as compared with that made in the bone-marrow."

The experimental work on the site of the formation of bile pigment has been directed largely toward the proof of such formation after the removal of the liver. The earliest work of this kind was done by Muller,<sup>25</sup> in 1844, on frogs, and later by Kunde<sup>26</sup> and by Moleschott.<sup>27</sup> All of these experimenters removed the livers of the frogs and in no case did they observe thereafter the formation of bile pigment. The experiments of Minkowski and Naunyn on geese have been described. The earliest efforts to exclude the liver in mammals were those of Whipple and Hooper,<sup>28</sup> who ligated the principal blood vessels to the liver in dogs and found that the subsequent intravenous injection of hemoglobin was followed by the development of jaundice in the tissues.

21 Van den Bergh, A. A. H., and Snapper, I. Ueber anhepatische Gallenfarbstoffbildung, *Berl. klin. Wchnschr.* **2** 1081, 1915.

22 Rich, A. R., and Rienhoff, W. F., Jr. The Bile-Pigment Content of the Splenic Vein, *Bull. Johns Hopkins Hosp.* **36** 431, 1925.

23 Mann, F. C., Bollman, J. L., Sheard, C., and Baldes, E. J. The Site of the Formation of Bilirubin, *Am. J. Physiol.* **74** 497, 1925.

24 Mann, F. C., Sheard, Charles, and Bollman, J. L. An Evaluation of the Relative Amounts of Bilirubin Formed in the Liver, Spleen and Bone Marrow, *Am. J. Physiol.* **78** 384, 1926.

25 Muller, J. *Handbuch der Physiologie des Menschen fur Vorlesungen*, Coblenz, J. Holscher, 1840-1844, vol. 4, p. 131.

26 Kunde, F. T. *De hepatis ranarum extirpatione*, Berlin, Schlesinger, 1850.

27 Moleschott, J. *Untersuchungen uber die Bildungsstatte der Galle*, *Arch. f. physiol. Heilk.* **11** 479, 1852.

28 Whipple, G. H., and Hooper, C. W. Hematogenous and Obstructive Icterus. Experimental Studies by Means of the Eck Fistula, *J. Exper. Med.* **17** 593, 1913.

ment, but that in dogs, when similar experiments were made, bile pigment could not be demonstrated in the tissues. Nevertheless, dogs were used almost exclusively in the later experiments because they survived more extensive surgical procedures than did rabbits. They were the subjects of most of the experiments on the formation of bilirubin in mammals.

Zenker's fluid was found to be the best fixative for general use, although Boun's fluid showed bile pigment in the tissues of jaundiced rabbits more clearly than did any other fixative. A diluted solution of formaldehyde U S P (1:10) was slightly inferior to Boun's fluid. Parts of all tissues taken were fixed in Zenker's fluid, and in more than half of the experiments similar pieces of tissue were also fixed in Boun's fluid or formaldehyde. Such tissues were embedded in paraffin and from them sections 7.5 microns thick were cut.

Another method was to macerate the fresh tissues in Pacini's fluid consisting of 5 per cent mercuric chloride in physiologic solution of sodium chloride. With this method, Lowit<sup>36</sup> had been able to demonstrate bile pigment by the microscopic Gmelin reaction in the hepatic cells of frogs. These results could not be duplicated in the tissues of dogs, except in the case of bile plugs filling the bile capillaries, which showed the typical play of colors with the Gmelin reagent in paraffin sections of livers from jaundiced dogs. Frozen sections of formaldehyde-fixed material were also studied with the Gmelin reagent and various stains. These methods, which rendered the use of alcohol unnecessary, eliminated the possibility that bilirubin was being extracted from the tissues by the alcohol used in dehydration.

Various combinations of stains were employed in the hope of demonstrating bilirubin or other products of hemoglobin disintegration in the tissues. Of the nonspecific stains, the combination of eosin and methylene blue (Methylthionine chloride, U S P), as described by Mallory and Wright,<sup>37</sup> gave a striking demonstration of a yellowish-brown pigment occurring normally in the spleen and the bone-marrow. This pigment was barely distinguishable in sections stained by the hematoxylin and eosin method, which has such widespread use. Mallory's triple connective tissue stain (acid-fuchsin, orange G and aniline blue) also showed these masses of pigment, although the cytologic details were not clear.

One of the products of hemoglobin disintegration has long been known to give a specific reaction for iron. Three microchemical specific iron stains are in common use: ammonium sulphide, potassium ferrocyanide and hydrochloric acid (the Berlin blue or Prussian blue reaction), and potassium ferricyanide and hydrochloric acid (Turnbull's blue). After many trials, the Berlin blue method was selected, because it gave a characteristic deep blue color to any iron present in the tissues. Various counterstains can be used with these iron reagents. Basic fuchsin, the usual stain employed with potassium ferrocyanide, was abandoned in favor of alum carmine, because the faint red nuclear stain given by the latter provided a better contrast to the deep blue of the iron-containing pigment.

The method finally adopted was as follows. Sections of tissues fixed in Zenker's fluid, formaldehyde or Boun's fluid were treated with potassium ferrocyanide and hydrochloric acid for thirty seconds at 70°C, as described by Mallory and Wright. The sections were then washed and counterstained for twenty minutes in alum carmine warmed to 50°C. In this way, iron was stained a dark

36 Lowit M. *Beitrage zur Lehre vom Icterus, Beitr z path Anat u z allg Path* 4:223, 1889.

37 Mallory, F B, and Wright, J H. *Pathological Technique*, ed 8, Philadelphia, W B Saunders Company, 1924.

organs The other reticulo-endothelial cells are also concerned in iron metabolism

A microscopic study of the occurrence of iron in the spleen as compared with that in the liver in domestic animals was recently made by Ziegler and Wolf<sup>33</sup> They found much iron in the spleen of the horse, cow and sheep and a smaller amount in the spleen of the dog and swine The iron occurred chiefly in the reticular cells of the spleen, although traces were seen in the capsule and the trabeculae Small amounts of iron were sometimes found in the livers of all the species studied The iron, when found in the liver, was always limited to the endothelial (Kupffer) cells The bone-marrow was not studied

Interesting observations were made by Peabody and Broun<sup>34</sup> on the phagocytosis of erythrocytes in the bone-marrow The phagocytic cells probably should be classified as "endothelial leukocytes," although whether they arise from the vascular endothelium or from the reticulum has not been proved These workers, employing the Berlin blue iron reaction, observed in the bone-marrow the presence of erythrocytes and granules of iron in the same phagocyte They concluded that the phagocyte of the bone-marrow ingests erythrocytes and that the hemosiderin (an iron-containing substance) is formed from hemoglobin within the phagocyte

Corr<sup>35</sup> recently studied material from seventy-one necropsies with respect to the distribution of hemosiderin and bilirubin Sections of liver and spleen and occasionally of bone-marrow, kidney, lymph node lung, suprarenal gland and pancreas were stained for iron by the Berlin blue method Hemosiderin was found in varying amounts in the splenic phagocytes, in the hepatic and Kupffer cells of the liver and in the reticulo-endothelial cells of the bone-marrow Corr concluded that the reticulo-endothelial cells of the spleen and the bone-marrow were most active in breaking down the hemoglobin He believed that the Kupffer cells and large wandering phagocytes served as a reserve of the reticulo-endothelial system

#### TECHNIC

Dogs and rabbits were used in the preliminary experiments It was found that in rabbits, when jaundice had been produced experimentally by ligation of the common bile duct and cholecystectomy, the tissues frequently contained bile pig-

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33 Ziegler, M, and Wolf, E Histochemische Untersuchungen uber das Vorkommen eisenhaltigen Pigments (Hemosiderins) in der Milz und Leber der Haussaugetiere unter normalen und einigen pathologischen Verhaltnissen, Virchows Arch f path Anat **249** 374, 1924

34 Peabody, F W, and Broun, G O Phagocytosis of Erythrocytes in the Bone Marrow, with Special Reference to Pernicious Anemia, Am J Path **1** 169, 1925

35 Corr, Philip Histochemical Evidence Concerning the site of the Formation of Bile Pigment, Arch Path **7** 84 (Jan) 1929

A wide variation in the iron content of the liver was found in normal dogs. The iron-containing pigments appeared solely in the stellate (Kupffer) cells of the sinusoids of the liver. The pigment usually occurred in the form of clustered droplets, and a faintly blue stain was found in many of the stellate cells. An iron-containing pigment was not seen in any of the parenchymal, or hepatic, cells. Small amounts of iron were found in the various lymph nodes, as will be discussed later.

#### EXPERIMENTS

In the first series of experiments, the dogs were anesthetized and pieces of liver, spleen, bone-marrow, lymph nodes and various other tissues were removed. The hemolyzed corpuscles from 100 cc of dog's blood were injected into the jugular vein. At intervals of from fifteen minutes to three hours thereafter, additional pieces of the same organs were excised. Samples of blood from the jugular vein, corresponding in time to the various sets of tissues removed, were studied by the spectrophotometric method devised by Sheard, Baldes, Mann and Bollman,<sup>38</sup> to determine the quantity of bilirubin in the circulating blood at the various stages of the experiment. The protocols of three typical experiments are given.

EXPERIMENT 1—A dog weighing 27.3 Kg. was anesthetized with ether at 3:05 p. m. and pieces of the liver, spleen, bone-marrow (right femur) and mesenteric lymph node were removed. Fifteen cubic centimeters of blood was withdrawn from the jugular vein for the determination of bilirubin. At 3:10 p. m., the laked corpuscles from 100 cc of the blood of another dog were injected into the jugular vein. This solution was made isotonic by the addition of sodium chloride and was warmed to 37°C. At 3:25 p. m., a piece of bone-marrow (right humerus) was removed. At 3:40 p. m. pieces of liver, spleen and bone-marrow (left femur) were removed, and 15 cc of blood was withdrawn from the jugular vein. At 4:10 p. m., pieces of liver, spleen, bone-marrow (left humerus), retrosternal lymph node and mesenteric lymph node were removed and 15 cc of blood was withdrawn from the jugular vein. The animal was killed. The results of the postmortem examination were negative.

Spectrophotometric studies of the samples of blood, by the method described by Sheard, Baldes, Mann and Bollman, showed a marked increase in bilirubin content during the course of the experiment. This was indicated by increased absorption in the region of wave length 500 to wave length 430, due to the bilirubin in the acetone-alcohol solution of the blood sample. At wave length 430, the first sample showed 75 per cent transmission, the second showed 51 per cent and the last showed 50 per cent.

The tissues removed during the experiment were fixed in Zenker's fluid, sectioned in paraffin and stained by the Berlin blue method. A study of these sections did not show any recognizable change in the quantity of iron-containing pigment in the liver, spleen and mesenteric lymph nodes. A section of the bone-marrow removed before the injection of hemoglobin contained a small amount of iron. A similar section taken one hour after the injection of the hemoglobin had more than twice as much of the iron-containing pigment. This increase occurred chiefly in the form of tiny greenish-blue droplets, or clusters of droplets, which were

<sup>38</sup> Sheard, Charles, Baldes, E. J., Mann, F. C. and Bollman, J. L. Spectrophotometric Determinations of Bilirubin, *Am. J. Physiol.* **76**: 577, 1926.

or light blue depending on its concentration in the cell, the nuclei were stained red and the cytoplasm, in general, a faint pink. Erythrocytes were stained a faint yellowish green.

#### IRON-CONTAINING PIGMENTS AS SEEN NORMALLY IN BONE-MARROW, SPLEEN AND LIVER

Before the various experiments are described, it is advisable to present the picture normally seen in the bone-marrow, spleen and liver. Such tissues were embedded in paraffin and stained with Berlin blue and alum carmine to demonstrate the occurrence of iron-containing pigment. In the bone-marrow (fig 1), this pigment was seen in the form of dark

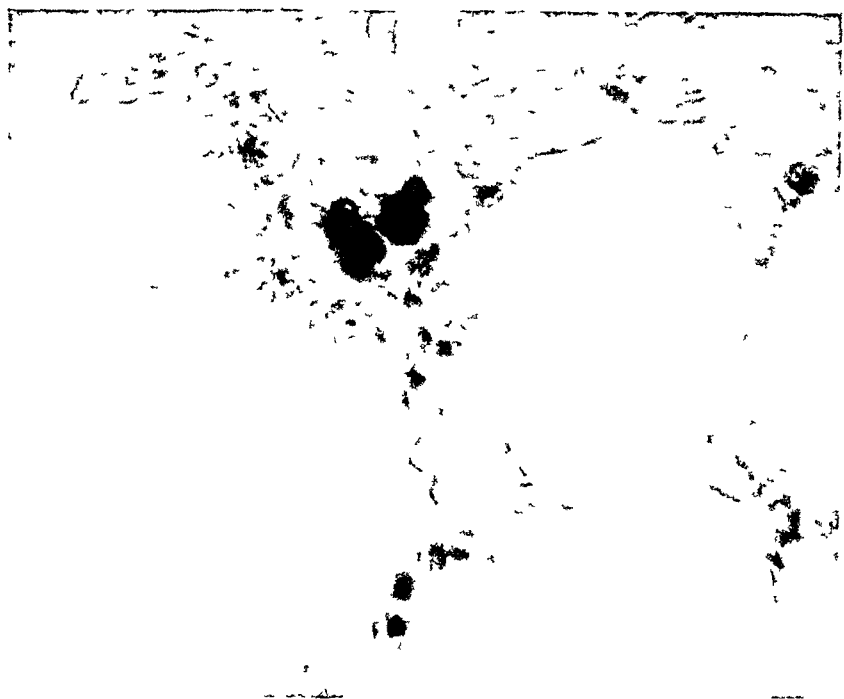


Fig 1—Bone-marrow before injection of hemoglobin,  $\times 1,000$ . The section shown here and in subsequent figures were all stained for iron by the Berlin blue method.

masses which were actually blue in the section, but which photographed black with a red screen. The masses lay as single droplets or clusters of droplets in large cells of reticular type, which were seen between fat droplets and mingled with the other cellular elements of the bone-marrow. Such cells often showed a diffuse faintly blue stain in addition to the dark blue droplets.

A section of the spleen likewise showed large numbers of the dark masses, which were found in the large phagocytic cells usually called splenic cells. A diffuse faintly blue stain also was seen in some of these cells. None of the iron-containing pigment was found in the malpighian corpuscles.



The spleen contained a moderate amount of iron before the injection of the hemoglobin, and a noticeable increase did not occur during the course of the experiment. The samples of blood from the jugular vein were studied by the spectrophotometric method. A marked increase in the bilirubin in the serum was shown by the percentage of transmission at wave length 430, this was 87 before the injection of laked blood and 57, 59 and 64 in the samples withdrawn following its injection.

In two experiments the animals were allowed to live six hours or longer after the injection of hemoglobin.

EXPERIMENT 3—A dog weighing 13.2 Kg. was etherized and pieces of liver, spleen and bone-marrow were removed before and one hour after the intravenous

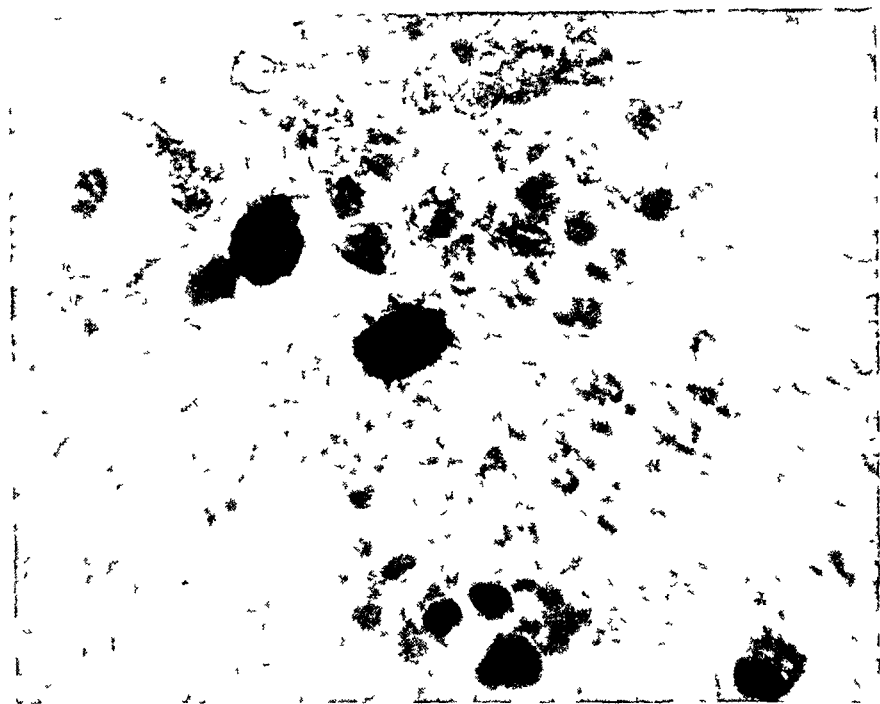


Fig 3—Bone-marrow two hours after injection of hemoglobin,  $\times 1,000$

injection of laked corpuscles. The incisions were then closed. Five hours later the animal appeared to be in good condition, but died during the night. The results of the necropsy twenty-two hours after the injection of laked blood were negative, except for the presence of about 30 cc of thick bloody fluid in the peritoneal cavity. The usual tissues were removed for study.

Under the microscope in the first series, a small amount of iron-containing pigment was seen in the liver and the mesenteric lymph node, and comparatively small quantities in the spleen and the bone-marrow (fig 4). In the other two series there was little, if any, change in the liver, spleen and lymph nodes, while the iron content of the bone-marrow was about doubled. In the bone-marrow (fig 5), one hour after hemoglobin was injected, there was seen to be a marked increase in the number of greenish-blue droplets, which appeared to be the form that the hemoglobin assumes when it is first taken up by the reticular cells. The bone-marrow (fig 6), from six to twenty-two hours after the injection of hemo-

always found lying within reticular cells of the bone-marrow. When these tissues were studied unstained, or stained by the eosin and methylene-blue method, the intracellular droplets were an orange-yellow, and were the only pigments appearing in the sections.

EXPERIMENT 2—This experiment was similar to experiment 1, although covering a slightly longer period of time. A dog weighing 22 Kg. was etherized, and pieces of liver, spleen and bone-marrow were removed, after which the laked corpuscles from 100 cc. of dog's blood were injected into the jugular vein. Additional pieces of the same organs were excised at intervals of thirty minutes, one hour, two hours and three hours after the injection of laked blood. At the same time, blood was withdrawn for the determination of the serum bilirubin.

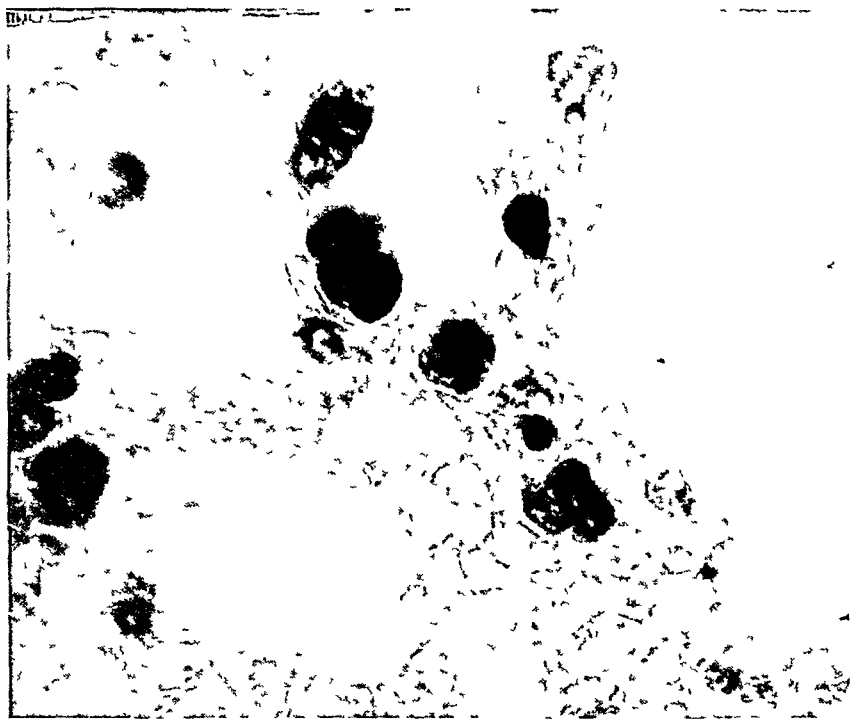


Fig 2—Bone-marrow thirty minutes after injection of hemoglobin,  $\times 1,000$

Examination, by the Berlin blue method, of the tissues removed in the course of the experiment showed a moderate number of masses of iron-containing pigment lying in reticular cells of the bone-marrow before the injection of hemoglobin (fig 1). The specimen of bone-marrow removed thirty minutes after the injection of hemoglobin contained about three times as much of this pigment, which appeared as grapelike clusters of greenish-blue droplets and was intracellular (fig 2). Figure 3 shows the condition of the bone marrow two hours after the hemoglobin was injected. Here about twice as much iron-containing pigment was seen as at the beginning of the experiment. Bone-marrow removed after three hours also showed a marked increase in the pigment.

The liver, prior to the injection of hemoglobin, showed small amounts of iron confined almost entirely to the tissues of the periportal spaces. The amount of iron pigment increased slightly two hours after the hemoglobin was injected, and the increase was more marked after three hours. Then small quantities of iron could be seen in occasional stellate cells, and more in the periportal spaces.

globin, contained similar droplets which stained a deeper blue, suggesting that more free iron had been liberated from engulfed hemoglobin. Such deep blue droplets were seen in most sections of normal bone-marrow.

Determinations of the serum bilirubin showed marked increase in bile pigment in the circulating blood after one hour, and a less degree of bilirubinemia after from six to twenty-two hours. At wave length 430, the first sample gave 85 per cent transmission, the second gave 20 per cent transmission and the last 51 per cent transmission.

Experiments 1, 2 and 3 were selected from a group of nine because in them the results were most striking. In three other experiments there was a definite, although moderate, increase in the amount of iron-

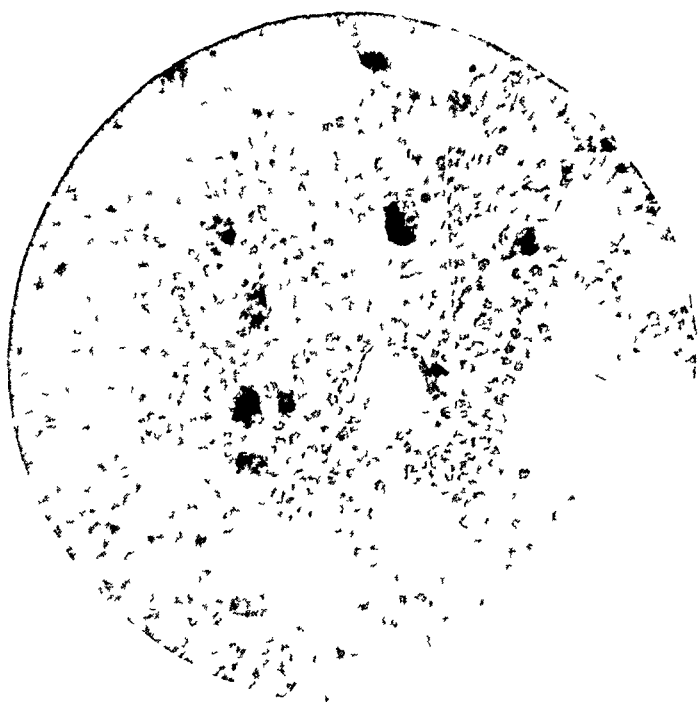


Fig 6—Bone-marrow from six to twenty-two hours after injection of hemoglobin,  $\times 200$

containing pigment in the reticular cells of the bone-marrow, in the remaining three experiments, a difference could not be detected between the bone-marrow before and that after the injection of hemoglobin. With the exception of that occurring in the first experiment, there was little, if any, change in the iron content of the liver. As a rule, the picture in the spleen remained the same after the injection of hemoglobin as before, although in one experiment an apparent slight increase in iron was noted. Since considerable amounts of iron are usually scattered diffusely through the splenic pulp, it is impossible to say with certainty from a microscopic study that an increase in the iron content did not occur.

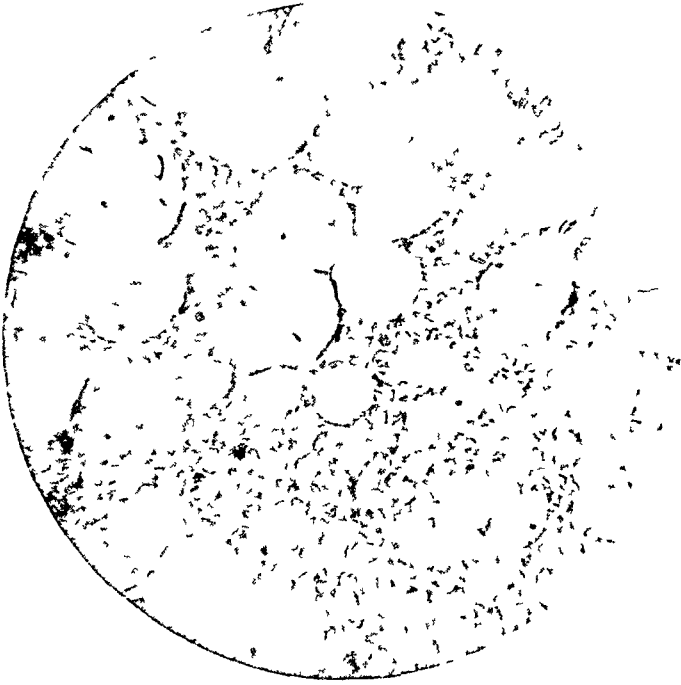


Fig 4—Bone-marrow before injection of hemoglobin,  $\times 200$

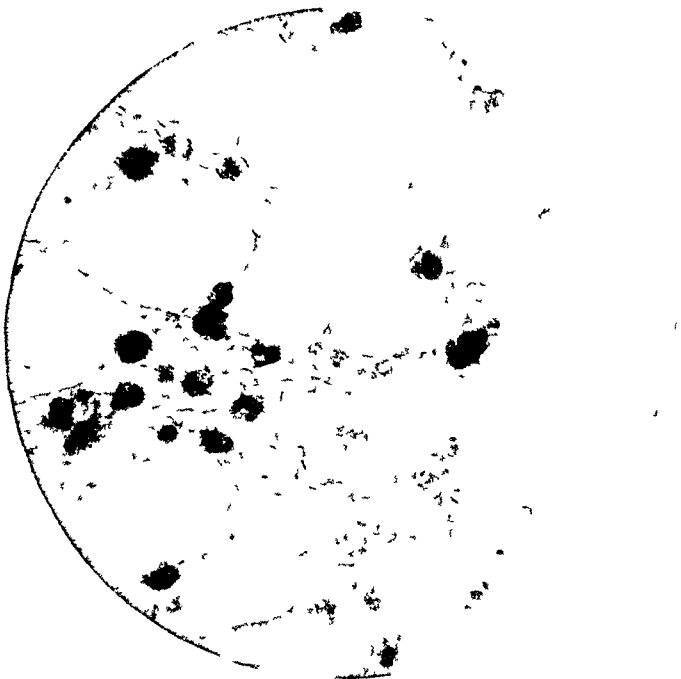


Fig 5—Bone-marrow one hour after injection of hemoglobin,  $\times 200$

spleen and bone-marrow were removed from a dog weighing 15 Kg. Two hundred cubic centimeters of blood was withdrawn from the jugular vein, and additional pieces of the tissues were taken at necropsy following the animal's death from seven to twenty-two hours later. The amount of iron present in the different series of tissues did not show appreciable change. In a similar experiment, 250 cc of blood was withdrawn from a dog weighing 20 Kg. The tissues taken before hemorrhage were compared with those removed an hour later and with those removed forty-eight hours later. In this case also, the iron content of the liver, spleen and bone-marrow remained the same throughout the experiment.

In order to rule out, as an important factor, the influence of the operative procedure on the organs studied, two experiments were performed in which the pieces of liver, spleen and bone-marrow were removed at from thirty-minute to sixty-minute intervals up to two and a half hours, but in which laked blood was not injected. These tissues did not show definite change as regards iron content, thus indicating that the microscopic changes observed in previous experiments were entirely the result of the injection of hemoglobin into the blood stream.

In the aforementioned protocols of experiments little has been said of the lymph nodes and various other members of the reticulo-endothelial system. Pieces of mesenteric lymph nodes were removed during the course of most of the experiments. The sections invariably showed either small traces of iron or its complete absence, without difference between those pieces removed before and those removed after the injection of hemoglobin.

One or two small nodes were usually found adherent to the deeper surface of the sternum near its upper end. Such nodes were usually reddish brown and contained much blood, sometimes resembling hemolymph nodes and at other times true lymph nodes. In one animal, a blood vessel was demonstrated to be passing into such a node. The Berlin blue stain showed varying amounts of iron, as well as considerable coal dust, present in the medullary portions of these nodes. In many cases, the iron was present in relatively large quantities, although the site of these nodes rendered it impossible to obtain specimens from the same animal before and after hemoglobin had been injected. Bronchial lymph nodes contained moderate amounts of iron.

Other organs, namely, the thymus gland, pituitary gland, suprarenal gland, testis, ovary and kidney, were stained for iron. This substance was invariably absent except for occasional minute traces in the connective tissue of the ovary, where it probably had resulted from the hemorrhage into ruptured graafian follicles. Even after the injection of hemoglobin, the kidney remained free from demonstrable iron.

When one considers the wide distribution of the bone-marrow, it is not surprising that a third of the experiments failed to show an increased content of iron following the injection of hemoglobin. Only a tiny fragment of marrow was examined and one can merely guess at the changes going on in the remainder of the skeleton. It is significant, however, that in none of the cases did sections of bone-marrow taken after such an injection show a decrease in iron content. One is justified, therefore, in attributing the increased iron content of the bone-marrow in the cited cases to the injection of hemoglobin. This substance is taken up by the reticular cells of the bone-marrow, in which it breaks down, with the liberation of iron and the formation of bilirubin or an intermediary product. Probably the bilirubin passes into the circulating blood as rapidly as it is elaborated and, for this reason, is never deposited in the tissues in a demonstrable form.

Two experiments were carried out in much the same way as those described except that the 100 cc of laked blood was injected into a tributary of the portal vein instead of into the jugular vein, thus forcing the hemoglobin to pass through the liver before it reached the bone-marrow and the spleen. In both experiments, the blood serum showed a high degree of bilirubinemia after from one to two hours. A slight increase in iron content occurred in the liver, without any definite change in the spleen. In one experiment there was a moderate increase of iron-containing droplets in the bone-marrow, a change was not seen in the bone-marrow in the other experiment. The jaundice may have been largely of an obstructive type owing to injury of the hepatic cells by the injection of hemoglobin into the portal vein.

In two other experiments, splenectomy was performed just prior to the injection of laked blood into the jugular vein. In one of the experiments observations for two and a half hours showed a marked rise in serum bilirubin. The tissues showed a slight increase in the iron content of the liver and a slight rise in the number of iron-containing droplets in the bone-marrow. The dog in the second experiment was allowed to live twenty-four hours and was then killed. Before splenectomy and the injection of hemoglobin, the liver contained a small amount of iron. Twenty-four hours later there was a marked increase in the iron-containing pigment in the stellate cells and occasionally in small periportal spaces. The bone-marrow showed a slight increase in iron-containing droplets. From these experiments, it would seem that removal of the spleen may cause the liver to assume a more prominent part than it usually does in the formation of bilirubin, although definite conclusions cannot be drawn from such limited data.

It was thought that a rapid loss of blood might cause a demonstrable decrease in the iron content of various tissues, since the rate of production of hemoglobin would probably be accelerated. Pieces of liver,

Studies on the formation of bilirubin in experimentally produced hematomas of the scalp were reported by van den Beigh. Such an experiment was performed for the purpose of studying the iron content of the tissues.

EXPERIMENT 5—A dog weighing 23.5 Kg. was anesthetized at 10 a. m., November 11, and 100 cc. of blood was withdrawn from the jugular vein into citrate solution and centrifugated, and the cells were washed with physiologic solution of sodium chloride. The cells were diluted with physiologic solution of sodium chloride to make 90 cc., which was injected as deeply as possible into the scalp over the right parietal bone. These steps were carried out with precautions to keep all solutions sterile. At 10 a. m., November 13, an attempt to aspirate

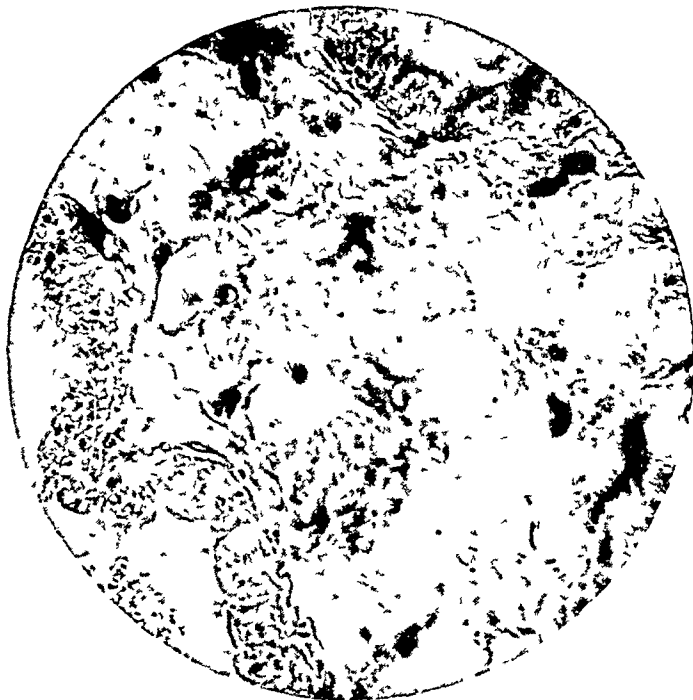


Fig. 7—Mediastinal tissue four days after the injection of hemoglobin into the pleural cavity. Two layers of pleural endothelium are seen at the periphery of the field. Iron appears in the connective tissue cells,  $\times 200$ .

fluid from the site of the injection was unsuccessful. One hundred cubic centimeters of laked blood was injected under the scalp over the left parietal bone. At 10 a. m., November 15, fluid could not be aspirated from the sites of injection. The animal was killed.

Small amounts of blood were found at the sites of injection, and considerable blood had gravitated into the cheeks. Pieces of tissue from the scalp were fixed, sectioned and stained by the Berlin blue method. The sections showed iron present in a large number of cells of the histiocyte type which lay in strands of connective tissue between the muscle bundles. The absence of iron from the muscle bundles themselves was apparent. In sections taken from the region of the right parotid gland, to which blood had gravitated, cells of the areolar tissue also were seen to contain iron.

The experiments of Hooper and Whipple, who injected laked blood or a solution of hemoglobin into the pleural cavities of dogs, were repeated. These authors found bilirubin present in quantities demonstrable by the Huppert-Salkowski test on the day following the injection of hemoglobin. They concluded that the transformation of hemoglobin into bilirubin is accomplished by the endothelium lining the pleural cavity. In the following experiment, their technic was employed.

EXPERIMENT 4—A dog weighing 7 Kg. was anesthetized at 2 p. m., November 16. Fifty cubic centimeters of blood was taken from another dog, the erythrocytes were washed with physiologic solution of sodium chloride and then laked with distilled water. This solution was diluted with physiologic solution of sodium chloride to make 400 cc. containing 0.6 per cent sodium chloride, which was injected into the right pleural cavity of the anesthetized animal. At 9 a. m., November 17, 60 cc. of dark red fluid was withdrawn from the right pleural cavity and centrifugated, and smears were made of the sediment. The supernatant fluid was divided into three portions. The first portion was examined by the spectrophotometric method, which proved unsatisfactory owing to the large amount of hemoglobin in the solution. A second portion gave a faint (questionable) indirect van den Bergh reaction for bile pigment. The other portion was subjected to the Huppert-Salkowski test, as used by Hooper and Whipple, it gave a faintly positive reaction. At 9 a. m., November 18, 50 cc. of laked erythrocytes in 200 cc. of 0.6 per cent sodium chloride solution was injected into the left pleural cavity. At 9 a. m., November 20, the animal was killed.

Necropsy revealed nothing abnormal except in the thoracic cavity, which did not contain free fluid. A brown fibrinous exudate covered the parietal pleura near both bases and over the diaphragm. A similar exudate and small black particles appeared on the mediastinal tissue between the heart and the diaphragm. Pieces of tissue from various points in the thoracic cavity were fixed, sectioned and stained by the Berlin blue method.

Smears from the aspirated pleural fluid showed large numbers of erythrocytes and polymorphonuclear leukocytes, in which iron could not be demonstrated. Fixed sections of the fibrinous exudate taken at necropsy showed traces of iron in a few cells resembling the large mononuclear leukocytes of the blood. The most significant observation in this experiment was the presence of iron in many connective tissue cells of the mediastinal tissue (fig. 7). Large numbers of stellate cells with large oval nuclei (evidently belonging to the histiocyte or connective tissue macrophage group) were stained a characteristic blue in sharp contrast with the endothelial cells, which were free from any trace of iron. The iron-containing cells lay immediately subjacent to the surface layer of endothelium. A lymph node on the internal surface of the sternum and one on the posterior thoracic wall both contained large amounts of iron. A small quantity of iron was found in a peribronchial lymph node.

The results obtained in this experiment confirm the earlier work of Hooper and Whipple in so far as they show the presence of bile pigment in the pleural cavity following the injection of hemoglobin. However, it appears that instead of the pleural endothelium (or mesothelium) being the tissue concerned, as these authors assumed, the cells of the subendothelial connective tissue converted the hemoglobin into bilirubin.



bone-marrow, spleen and liver contained, in varying amounts, an orange-yellow pigment which gave the characteristic Berlin blue reaction of iron. Since it is known that iron is liberated in the breaking down of hemoglobin into bilirubin, it is reasonable to conclude that the cells that contain iron are those concerned in the conversion of hemoglobin into bilirubin, or at least into a precursor of bilirubin. Furthermore, when samples of the various tissues are removed before the intravenous injection of hemoglobin and at regular intervals of time thereafter, it may be justifiably assumed that the tissues showing a striking increase in iron content (namely, the bone-marrow) are those actively concerned in the process of converting hemoglobin into bilirubin, while those tissues containing a constant amount of iron (as the spleen) probably have to do with storage of the iron until it is again built up into hemoglobin.

Various objections can be raised to the methods used and the conclusions drawn. It is unfortunate that a microscopic demonstration cannot be given of every step in the conversion of the hemoglobin molecule into bilirubin. Instead, one must fill in the gaps with the aid of information obtained by other workers who approached the problem with other methods. The results obtained harmonize well with those reported by experimenters who removed various organs, and by those who studied the blood flowing to and from these organs and tissues. From a review of the various types of cells that contain an increased amount of iron following the injection of hemoglobin (reticular cells of the bone-marrow, stellate cells of the liver and histiocytes in the thoracic wall and scalp), it is seen that these cells are all a part of the reticulo-endothelial system.

#### CONCLUSIONS

The Berlin blue method for the demonstration of iron-containing pigment in the tissues provides a means of identifying the cells that are concerned with at least one stage of the conversion of hemoglobin into bilirubin.

By the aforementioned method it has been shown that the intravenous injection of hemoglobin is often followed within an hour by a striking increase in the number of dioplets of iron-containing pigment in the reticular cells of the bone-marrow, and occasionally by a moderate increase of such pigment in the stellate cells of the liver.

The conclusion is drawn that the bone-marrow plays the major rôle in the formation of bilirubin, with the liver, spleen and possibly the lymph nodes having a lesser part in this process.

The connective tissue macrophages, or histiocytes, are probably responsible for the local formation of bilirubin resulting from the injection of hemoglobin into the pleural cavity or under the scalp.

In a similar experiment, the animal was killed sixteen days after laked blood had been injected under the scalp. Here also (fig 8) considerable quantities of iron could still be seen in the cells of the connective tissue lying between the bundles of muscle. Although in these experiments it was not possible to demonstrate the formation of bilirubin at the site of the injection of hemoglobin, one may assume from the experiments of van den Beigh, and of Makino,<sup>39</sup> that the hemoglobin underwent such a transformation. It would appear that the cells concerned in this process are the histiocytes, which belong to the same



Fig 8—Scalp sixteen days after local injection of hemoglobin. Iron is seen in the connective tissue macrophages,  $\times 600$

general system (reticulo-endothelial) as those cells which normally convert hemoglobin into bilirubin or its precursor in the bone-marrow, spleen and liver.

#### COMMENT

The experiments described in this report are the result of an attempt to use new methods in the study of an old problem, namely, the site of the formation of bile pigment. It was found that such tissues as the

<sup>39</sup> Makino, J. Beitrage zur Frage des anhepatocellularen Gallenfarbstoffbildung, Beitr z path Anat u z allg Path **72** 808, 1923-1924

Doan's observations on the effect of splenectomy were of universal application to the reaction to foreign substances in general or whether they applied only to the reaction to the specific substance sodium nucleinate. If the spleen has such a function as storing and then discharging leukocytes, it would be of as great significance as the mobilization of red cells by the spleen from its reservoir, in conditions of great need, as demonstrated by Barcroft.<sup>2</sup>

To determine this point, experiments were carried out, the effect of splenectomy being observed on the peripheral leukocyte count following injections of bacterial vaccines, and the results being compared with those following injections of sodium nucleinate.

#### EXPERIMENTAL PROCEDURE

Vaccines were prepared by suspending twenty-four hour cultures of *B. coli* on agar in 0.9 per cent sodium chloride and killing by heat. The same suspension was used in 1 cc doses in all rabbits, into which injections were made. This dosage caused no obvious symptomatic or circulatory changes in the rabbit, and was well tolerated in repeated doses.

Sodium nucleinate (Merck) from yeast nucleic acid, the same product as used by Doan, was dissolved in distilled water in 10 per cent solution. Two lots were used, both being negative to the biuret reaction. In addition, injections were made into one animal of nucleic acid (Merck) to which sodium hydroxide had been added until solution was effected and was faintly alkaline with phenolphthalein.

Curves of the leukocyte counts of the blood from the ear were made preliminary to and following the intravenous injection of these substances. Splenectomy was carried out on eleven rabbits aseptically. At varying times following operation, the leukocyte response to vaccines was determined in one series of animals, and the response to sodium nucleinate in another series.

To avoid all possible emotional factors which cause a disturbance in the leukocyte count, the rabbits were kept as quiet as possible during the bleeding, on a small table or in a roomy box, which restrained them from running about, but which permitted them to remain in their natural positions without cramping. Leukocyte counts were made by the same person with the same counting apparatus throughout the course of the experiments. Counts were made only after a good flow of blood had been obtained, as experience had shown that counts made on the first drop of blood escaping when the blood flow is poor give figures that are entirely too high. When the ears are cold and cyanotic, as seen after large doses of sodium nucleinate, in the more or less stagnant blood, the leukocytes are likely to accumulate, as is evidenced by the fact that subsequent drops of blood show lower counts, which check each other satisfactorily. This is in accord with the observations of Shaw,<sup>3</sup> who found that when the rabbit's ears are cold, and the blood flow is slow, the leukocytes accumulate in the vessels and cause a higher count than

<sup>2</sup> Barcroft, J., Harris, H. A., Orshovats, D., and Weiss, R. A Contribution to the Physiology of the Spleen, *J. Physiol.* **60** 443, 1925. Barcroft, J., and Stephens, J. G. Observations upon the Size of the Spleen, *ibid.* **64** 1, 1927.

<sup>3</sup> Shaw, A. F. B. The Influence of the Vasomotor State of the Peripheral Blood Vessels on the Leucocytic Content of the Blood, *J. Path. & Bact.* **29** 389, 1926.

# DOES SPLENECTOMY INFLUENCE THE LEUKOPENIA INDUCED BY THE INJECTION OF CERTAIN FOREIGN SUBSTANCES?<sup>2</sup>\*

ISOLDE T ZECKWER, M D

PHILADELPHIA

Doan, Zerfas, Warren and Ames<sup>1</sup> recently reported interesting experiments which suggest that the spleen may play a more important rôle in the redistribution of leukocytes within the body after injections of foreign substances than has hitherto been thought to be the case. Sodium nucleinate injected intravenously into a normal animal results in a marked leukopenia in the peripheral blood, which lasts for a number of hours, when it is succeeded by a leukocytosis. Doan and his co-workers expressed the belief that during the peripheral leukopenia the leukocytes have collected exclusively in the spleen, as indicated by leukocyte counts made on blood from the viscera, and they stated "That the spleen is solely responsible for the temporary depression of white cells in the general circulation under the conditions has been shown by splenectomy." They found that, "with the spleen eliminated from the rabbit, sodium nucleinate, under the conditions outlined, repeatedly produced a leukocytosis, without preceding leukopenia, within a period of time one half to one sixth of that required in animals in which the spleen was intact, the latter invariably showing a profound leukopenia immediately following the nucleinate injection." They indicated the importance of such a function of the spleen. "That the spleen may, under certain conditions, act as a temporary reservoir for myeloid white cells and thus exert something of a regulatory function, more or less beneficial, over their availability to the general circulation and tissues seems clear." They expressed the belief, however, that the "leukopenia of splenic origin after sodium nucleinate" may represent a disadvantage.

Since the peripheral leukopenia following the injection of sodium nucleinate seemed to resemble the peripheral leukopenia commonly observed after the intravenous injection of killed bacteria and other foreign substances, it seemed of importance to determine whether

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\* From the Department of Pathology, University of Pennsylvania Medical School

1 Doan, C A , Zerfas, L G , Warren, S, and Ames, O. A Study of the Mechanism of Nucleinate-Induced Leucopenic and Leucocytic States, with Special Reference to the Relative rôles of Liver, Spleen, and Bone Marrow, *J Exper Med* 47 403, 1928

*The Effect of the Injection of B Coli Vaccine and Sodium Nucleinate on the Leukocyte Count in the Peripheral Blood*

Animal	Date	Experimental Condition of the Animal	Agent Injected	Leukocyte Count Before Injection	Lowest Count After Injection	Hours After Injection When Leukocytes Began to Rise
R 1	9/13/28	Intact	1 cc of B coli vaccine	10,920	2,000	Between 3 and 4
	9/14/28	Splenectomy				
	9/19/28	5 days after operation	1 cc of B coli vaccine	16,400	2,700	Between 2 and 2½
	9/26/28	Infection, 12 days after operation	1 cc of B coli vaccine	22,800	2,600	Between 2 and 3½
R 2	9/13/28	Intact	1 cc of B coli vaccine	9,100	1,000	No rise by 5½ Between 2 and 3
	9/19/28	Intact	1 cc of B coli vaccine	8,400	4,400	
	9/24/28	Intact	1 cc of B coli vaccine	8,400	2,800	
R 3	9/17/28	Intact	1 cc of B coli vaccine	10,600	2,000	Between 3¼ and 4½
	9/20/28	Splenectomy				
	9/24/28	4 days after operation	1 cc of B coli vaccine	12,900	1,200	Between 2¼ and 2¾
R 4	9/17/28	Intact	1 cc of B coli vaccine	14,520	3,520	Between 5 and 6½
	9/21/28	Intact	1 cc of B coli vaccine	11,800	3,800	
R 5	10/ 5/28	Splenectomy				
	10/10/28	14 days after operation	1 cc of B coli vaccine	6,920	1,600	
	10/24/28	19 days after operation	1 cc of B coli vaccine	6,640	1,050	
R 6	9/27/28	Splenectomy				
	10/17/28	20 days after operation	1 Gm of nucleic acid + sodium hydroxide	10,400	3,200	No rise by 4½
R 7	10/ 5/28	Splenectomy				
	11/22/28	48 days after operation	0.1 Gm of sodium nucleinate	16,800	2,040	Between 1½ and 2
	12/ 7/28	63 days after operation	1 Gm of sodium nucleinate	11,240	1,940	Between 4½ and 5
	1/ 2/29	89 days after operation (Sodium barbital anesthesia)	1 Gm of sodium nucleinate	9,200	2,700	No rise at 1¼
R 8	11/ 5/28	Intact	0.5 Gm of sodium nucleinate	8,200	3,800	No rise by 1¼
	11/ 8/28	Intact	0.1 Gm of sodium nucleinate	13,650	2,150	Between 5 and 6
	12/12/28	Intact	0.1 Gm of sodium nucleinate	7,400	1,200	Between 3¼ and 3¾
	12/21/28	Splenectomy				
	1/ 3/29	13 days after operation	0.1 Gm of sodium nucleinate	9,000	1,000	Between 4 and 4½
	1/17/29	27 days after operation (Sodium barbital anesthesia)	0.1 Gm of sodium nucleinate	7,450	1,800	
R 9	11/ 6/28	Splenectomy				
	11/13/28	7 days after operation	0.1 Gm of sodium nucleinate	8,150	2,950	No rise at 1¼
R 10	11/ 6/28	Splenectomy				
	11/13/28	Infection, 7 days after operation	0.05 Gm of sodium nucleinate	24,600	9,060	
	11/20/28	Infection, 14 days after operation	0.1 Gm of sodium nucleinate	27,000	2,600	Between 1 and 2
R 11	11/27/28	Intact	0.5 Gm of sodium nucleinate	7,060	900	Between 6 and 7
	12/ 5/28	Intact	0.5 Gm of sodium nucleinate	10,000	1,940	Between 5 and 5½
	12/ 6/28	Splenectomy				
	12/11/28	5 days after operation	0.5 Gm of sodium nucleinate	14,900	2,300	Between 3 and 3½
R 12	11/26/28	Intact	0.1 Gm of sodium nucleinate	8,920	1,500	Between 5½ and 6
	12/ 3/28	Intact	0.1 Gm of sodium nucleinate	8,900	1,400	Between 5¼ and 5½
	12/ 6/28	Splenectomy				
	12/11/28	5 days after operation	0.1 Gm of sodium nucleinate	7,900	800	Between 6 and 6¾
	1/31/29	28 days after operation (Sodium barbital anesthesia)	0.1 Gm of sodium nucleinate	8,200	1,200	No rise at 3½
R 13	12/ 4/28	Intact	0.1 Gm of sodium nucleinate	8,740	1,000	Between 3½ and 4
	12/12/28	Intact	0.1 Gm of sodium nucleinate	10,000	1,400	Between 5¾ and 6
	12/21/28	Splenectomy				
	1/ 2/29	12 days after operation	0.1 Gm of sodium nucleinate	11,000	3,400	Between 2½ and 3

when the blood flows at normal velocity. He also found that pressure or "milking" a constricted vessel caused an increase in the leukocyte count.

After preliminary leukocyte counts were made, the intravenous injection was given, following which leukocyte counts were made at frequent intervals throughout the day. All counts were made on the blood from one ear, while the other ear was used for the intravenous injection. The experiments were all begun at about the same time of day, and the animals were fasted since the day before.

Autopsies on splenectomized animals showed no accessory splenic tissue.

In three splenectomized animals, blood pressure tracings were made with the animals under sodium barbital anesthesia (0.4 Gm per kilogram of body weight), simultaneous leukocyte curves being made.

## RESULTS

### *Leukocyte Changes Following the Injection of B coli Vaccine—*

(a) The Effect of Splenectomy on the Degree of Leukopenia. The leukocyte curves following the injection of *B coli* vaccine were compared in two animals (R 1 and R 3, table) before and after splenectomy. A rapid fall in leukocytes to a low level occurred after each injection, whether the spleen was present or absent, even when, as on one occasion, a high initial leukocyte count was present due to infection (R 1). A third rabbit (R 5), in which no curve had been determined before splenectomy, showed on two occasions a profound leukopenia fourteen and nineteen days after splenectomy.

Usually the leukocytes fell to about the same level, whether the bacterial injection was a first injection or a repeated dose, or whether the spleen was present or had been removed. On two occasions, once in an intact rabbit (R 2) and once in a splenectomized rabbit (R 3), however, the leukocytes did not fall to such a low level as they had on a previous injection in the same animal. Consequently, any demonstration that splenectomy causes an alteration in the degree of leukopenia would have to be controlled by determining the range of variation in a large series of intact animals. No such quantitative comparison was attempted in these experiments. For the present purpose, merely the demonstration that a marked leukopenia occurred in the absence of the spleen was considered sufficient.

From the total leukocyte counts and the differential count, the number of granular and nongranular cells was calculated. When the total leukocyte count dropped, the number of polymorphonuclear cells fell nearly to zero and that of the lymphocytes fell appreciably. When the total leukocyte count rose, this rise was due largely to young forms of polymorphonuclear cells, and the lymphocytes remained at a low level and did not rise during the course of the experiment. The rise in leukocytes was due then to new cells being discharged from the marrow, not to the original leukocytes being returned to the circulation. The same distribution of cells occurred whether the rabbits were splenectomized or intact.

at times following splenectomy varying from four to eighty-nine days. Just as with injections of *B. coli*, there could not be made out any clearcut difference in the degree of leukopenia depending on whether it was the first injection or a repeated injection, or whether the spleen was present or had been removed. Even in the presence of a high leukocyte count due to infection in R 10, the leukocyte fall was pronounced. In fact, the higher the leukocyte count, the more spectacular is the fall. With the doses of 1 Gm. it was difficult to get representative samples of blood. The blood as first secured from the puncture was deep purple and viscid. Attention has been called previously to the fact that such blood does not permit a valid count. As concrete illustrations of this, in the splenectomized rabbit R 7, one hour after the injection of sodium nucleinate, a count made on the stagnant blue blood was 4,600 cells, while a moment later, when a good flow had been secured, the count was 2,700.

(c) The Effect of Splenectomy on the Time of the Rise of Leukocytes After the Leukopenic Period. In the experiments of Doan and his associates, they stated that splenectomy results in a rise in leukocytes after injections of sodium nucleinate within a period of time from one half to one sixth of that required in animals with spleens intact. Perhaps the results in one group of splenectomized rabbits were being compared with those in a control group of intact animals rather than the curves in the same animals before and after splenectomy, as the charts of the splenectomized animals show no curves previous to the operations, except that in one chart the curve after partial splenectomy was compared with that after complete splenectomy in the same rabbit.

In the present experiments, the time of rise in leukocytes was found to differ so greatly in different intact animals that it would seem to be necessary to have a large series of normal and test animals, in order to establish means of the two series which could be compared for a significant difference. Instead of running such a large series, it was thought advisable to determine at least two curves before splenectomy in several animals, and to compare these results with curves after splenectomy in the same animals. This would control the effect of repetition of the injection and would also control the factor of individual variation in different animals. The accompanying table shows the results thus obtained in R 8, R 11, R 12 and R 13 (charts 1 and 2).

R 11 received two injections before splenectomy was performed. The second time a rise occurred nearly two hours sooner than on the first injection. The animal was then splenectomized. Five days after operation, on the injection of the same dose of sodium nucleinate, the rise occurred nearly two hours sooner than on the second injection. That

(b) The Effect of Splenectomy on the Time of Rise of Leukocytes after the Leukopenic Period, Following the Injection of Vaccine In R 1 and R 3 (table), the rise in leukocytes after the leukopenic period occurred sooner after splenectomy than in the same animals before splenectomy Doan and his co-workers had considered that an earlier rise in leukocytes after injection of sodium nucleinate was a result of splenectomy But in the case of injections of vaccine, in which the development of immunity must be considered, such a conclusion could not be reached without determining the effect of repeated injections per se

In an intact animal, R 2, two curves following the injections of vaccine were made six days apart The second injection resulted in a much earlier rise in leukocytes Consequently, the earlier rise obtained in R 1 and R 3 after splenectomy, as compared with that before operation, could not be attributed to splenectomy, but seemed to be merely the quicker response on the part of the leukocytes induced by the first injection

The results indicated that splenectomy had no such effect on the reaction to vaccine which was found by Doan and his associates to occur after injection of sodium nucleinate This conclusion necessitated a reinvestigation of the effect of splenectomy on the leukocyte changes following the injection of sodium nucleinate

*Leukocyte Changes Following the Injection of Sodium Nucleinate —*

(a) The Effect of Varying Doses of Sodium Nucleinate Doan used sodium nucleinate in doses of 1 Gm per rabbit In his charts it is indicated that he often used caffeine sodium benzoate with it Evidently, the animals required stimulants after this large dosage, as, from his description, the general constitutional reaction of the animals to this substance appears to be severe In the present experiments, doses of 1 Gm were used in two animals (R 6, R 7) without stimulants, but these animals were so prostrated by the dose that blood could be obtained only with great difficulty It was found that 0.1 Gm of sodium nucleinate per rabbit was effective in producing a leukopenia, and resulted in no obvious vascular changes, so that the animals could be bled readily, and this dosage was well tolerated by the animals, so that injections could be repeated frequently for comparison, without stimulants

(b) The Effect of Splenectomy on the Degree of Leukopenia In the present experiments, it was found that splenectomy did not prevent the occurrence of a marked degree of leukopenia following the intravenous injection of sodium nucleinate in doses of 1 Gm per rabbit (R 6, R 7), in doses of 0.5 Gm (R 11), and in doses of 0.1 Gm (R 7, R 8, R 9, R 10, R 12, R 13, table) In no animal was there found an absence of a marked degree of leukopenia, and this occurred



R 13 was the only rabbit that showed an earlier rise after splenectomy than at any time before splenectomy. In the present experiments, therefore, there was no clearcut evidence that splenectomy resulted in a more rapid return rise of leukocytes.

(d) The Changes in Blood Pressure Resulting from the Injection of Sodium Nucleinate. The question arose as to whether the difference

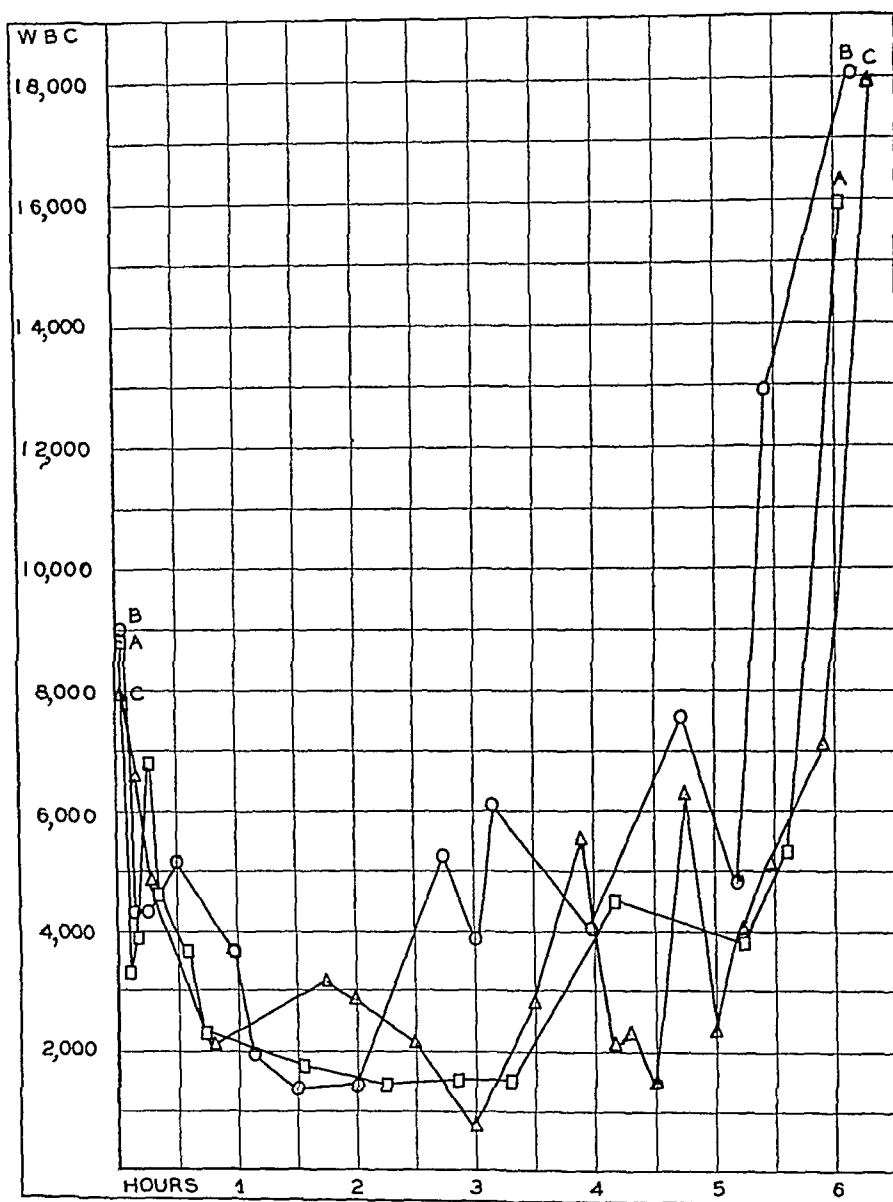


Chart 2—Leukocyte counts in rabbit 12 after the injection of sodium nucleinate. The curve marked *A* represents the count on November 26, after the injection of 0.1 Gm, with the animal intact, *B*, that on December 6, after the injection of 0.1 Gm, with the animal intact, and *C*, that on December 11, after the injection of 0.1 Gm, five days after splenectomy.

in results obtained by Doan and his associates and those recorded in the present experiments was dependent on differing conditions, such as changes in blood pressure occurring in the present experiments and not

is, the interval had not been shortened after splenectomy by any more than that by which the second response, when the spleen was intact, had been shortened over the first R 12, on the other hand, showed almost the identical interval on two occasions before splenectomy and at five days after splenectomy

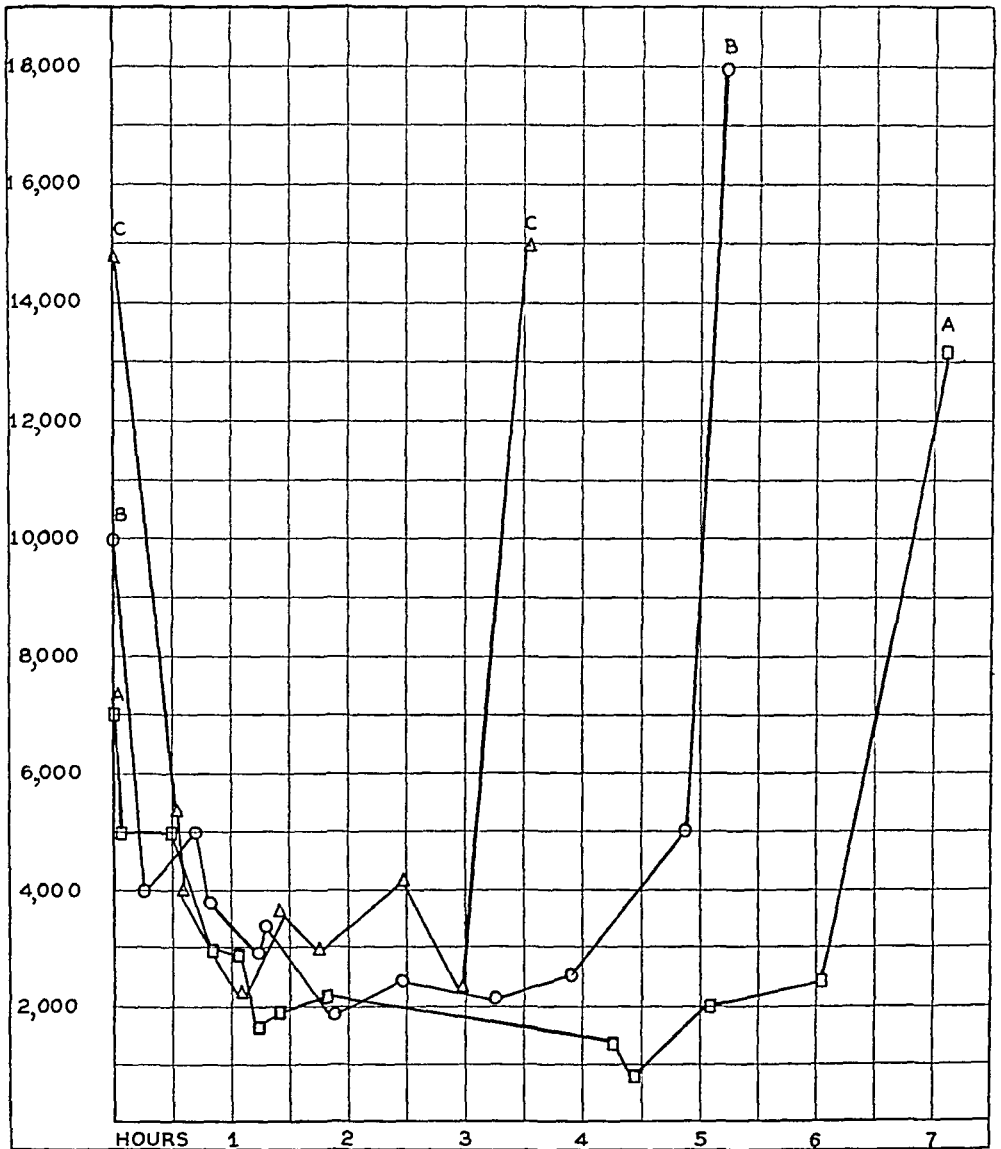


Chart 1—Leukocyte counts in rabbit 11 after the injection of sodium nucleinate. The curve marked *A* represents the leukocyte count on November 27, after the injection of 0.5 Gm., with the animal intact, *B* represents the count on December 5, after the injection of 0.5 Gm., with the animal intact, and *C*, that on December 11, after an injection of 0.5 Gm., five days after splenectomy.

R 8 showed a return rise in leukocytes about two hours sooner after the third injection before splenectomy than after the second. After splenectomy, the rise occurred later than on the third occasion before splenectomy.

In R 12, the smaller dosage, 0.1 Gm of sodium nuclemate, resulted in a temporary fall of blood pressure from 92 to 36 mm of mercury, but there was a rapid return to the previous level in nineteen minutes. For three and a half hours thereafter the blood pressure remained at the level at which it was previous to injection, the experiment was then terminated. The leukopenia occurred after the blood pressure had returned to normal, and was maintained, the counts varying from 1,200 to 1,800 cells during this entire period. Chart 3 represents the changes in blood pressure.

A similar result was obtained with the smaller dose in R 8, in which the blood pressure before injection was 110 mm. On the injection of 0.1 Gm of sodium nuclemate, the blood pressure fell temporarily to 40 mm, with a rapid return to the previous level in eleven minutes. The leukopenia was maintained for two and a half hours, during which time the blood pressure remained at the preliminary high level until the experiment was terminated.

In the present experiments, five rabbits were used for injections of *B. coli* and eight for injections of sodium nuclemate. Three of the animals in the *B. coli* group and eight in the sodium nuclemate group were splenectomized. The uniformity of the results obtained made further experiments seem unnecessary. In Doan's experiments, "uncomplicated studies of the peripheral blood after sodium nuclemate were made in six rabbits," and splenectomy was performed in seven rabbits.

#### COMMENT

The literature on the problem of the redistribution of leukocytes within the body after the injection of various agents has been discussed fairly completely by Doan and his co-workers, so it need not be mentioned here. These authors emphasized the necessity of studying the living animal with the circulatory system functioning normally, and they believed that disregard of this is responsible for the conflicting data in previous experiments, many of which have been histologic studies of the tissues at death. In living rabbits under barbital anesthesia they found, during the period of peripheral leukopenia, lowered leukocyte counts in the blood from the liver and lungs and no evidence of the accumulation of leukocytes within these organs, but a marked accumulation in the spleen.

In the present experiments, no attempt was made to localize accurately the leukocytes during the period of peripheral leukopenia. That peripheral leukopenia was invariably demonstrated in splenectomized animals implies logically that the viscera or the vascular system in the splanchnic area provide for the temporary storage of leukocytes, and that such function completely compensates for whatever function the spleen possesses in this regard.

operating in Doan's experiments Doan reported that the blood pressure was recorded in one cat after an injection of 2 Gm of sodium nucleinate, a moderate rise was maintained for some time As no leukocyte counts are stated, it is not evident that a leukopenia occurred in this experiment with the dosage used Vasoconstriction and vasodilation occurred in the rabbits, and, as previously stated, these investigators often used caffeine sodium benzoate, which implies that the animals may have been in a state of considerable shock

Records of the blood pressure were made in splenectomized rabbits (R 7, R 8, R 12), with the animals under sodium barbital anesthesia

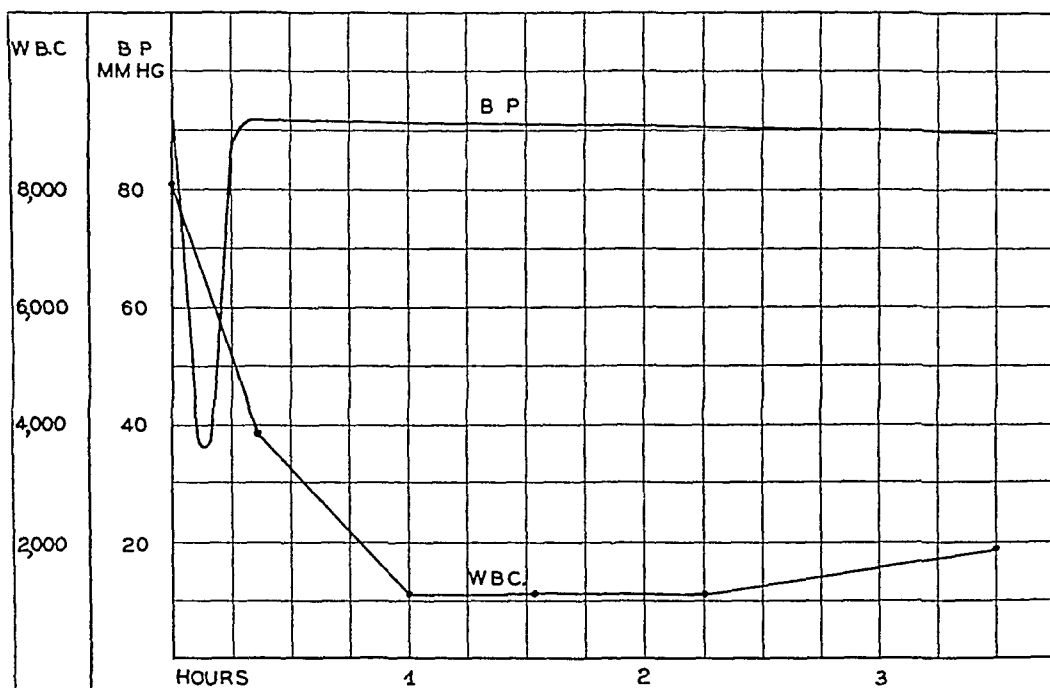


Chart 3—Leukocyte counts (W B C) and blood pressure (B P) following the injection of 0.1 Gm of sodium nucleinate into rabbit 12 (splenectomized)

(0.4 Gm per kilogram of body weight) Every precaution was taken to guard against complicating factors, so that the changes in blood pressure that occurred were the result of injections of sodium nucleinate per se Leukocyte curves of the blood from the vein of an ear were made at the same time

In R 7, the injection of 1 Gm of sodium nucleinate caused an abrupt fall in blood pressure from 80 to 30 mm of mercury The blood pressure continued at the same low level without any rise for one and a half hours, when the experiment was terminated The number of peripheral leukocytes fell to 2,700, but this probably does not represent the lowest level, as counts were not made frequently

# SOLITARY CYST OF THE KIDNEY\*

WILHELM C HUEPER, M D

CHICAGO

Solitary cysts of the kidney are one of the most uncommon conditions encountered in renal pathology. In a recent paper, Carson<sup>1</sup> collected reports of 151 cases from the literature. But Kairis,<sup>2</sup> who also reviewed the literature on this subject, stated that Laquière,<sup>3</sup> to whom Carson referred in his communication, erroneously included in his list of solitary cysts a number of cases which do not belong to this group, but which consist of echinococcus cysts, paranephritic cysts, cystic kidneys, traumatic blood cysts and other growths.

## SEX AND AGE

Solitary cysts are more often found in women than in men (Carson gave a ratio of 89:41). The same author notes further that they usually occur in persons from 30 to 60 years old (average age, 45). But they are occasionally seen in young persons and in old people.

## LOCATION AND MICROSCOPIC APPEARANCE

The cysts are in general unilateral and are more often located in the right kidney than in the left (Carson gave a ratio of 51:21). They may occupy the upper or the lower pole (Kairis found the cysts in the lower pole in two thirds of the cases) and are infrequently found in the anterior surface or the hilum.

They appear in the hypochondriac region as round or irregularly oval cystic formations attached with a more or less broad base to the kidney. They project into the abdominal cavity, where they are sometimes adherent to the adjacent organs. The surface is grayish white and smooth. The wall may be translucent. They vary in size from that of a hen's egg to that of a full term uterus (from 30 to 6,000 cc). Their average diameter is 15 cm (Carson). The thickness of the wall varies from 0.5 to 3 cm. The fibrous capsule of the kidney extends over the whole cyst and can often be separated from the cystic wall proper. The inner surface is smooth, grayish white and glistening.

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\* Submitted for publication, March 7, 1929.

\* From the Department of Pathology, Loyola University School of Medicine and the Laboratories of Mercy Hospital.

1 Carson. Solitary Cysts of the Kidney, *Ann Surg* **87**:250, 1928.

2 Kairis. Zur Kenntnis der solitären Nierencysten, *Arch f klin Chir* **149**:700, 1928.

3 Laquière. Kystes séreux du rein et opérations conservatrices, *J de chir* **26**:257, 1925.

The conflicting results of these experiments with those of Doan illustrate the complexity of factors which determine the leukocyte count in the peripheral blood at any moment. There is no suggestion that the actual quantitative data are not correct, in both instances, under the given experimental conditions. But how slight may be the difference in experimental conditions which may be responsible for varying results is clearly demonstrated. I have not been able to find any other work published on the effect of splenectomy on the redistribution of leukocytes which throws light on the factors that might explain the apparent discrepancy. I am inclined to believe that the differences in results may depend on the vasomotor state of the peripheral vessels, the use of caffeine perhaps determining the difference in Doan's experiments.

#### SUMMARY

Under the conditions of these experiments, splenectomy in rabbits had no effect in preventing the occurrence of the usual leukopenia which results from the intravenous injection of *B. coli* vaccine and of sodium nucleinate, and had no definite effect in hastening the return rise in the number of leukocytes after the leukopenic period.

this period the tubules normally pass through a cystic stage. He contended, therefore, that the persistence of this state during later life represents the cause of solitary cysts.

#### REPORT OF CASE

A woman, aged 53, came to autopsy after an acute illness of a few days. She had never complained of any abdominal symptoms. The autopsy showed a stout woman with a diffuse, bilateral, hemorrhagic bronchopneumonia, fatty degeneration of the heart, septic hyperplasia of the spleen, cloudy swelling of the liver and kidney, marked hyperemia of the meninges and the brain, two small polypi in the uterine cervix and a large solitary cyst of the left kidney and a small one of the right.

The solitary serous cyst of the left kidney was located in the upper pole and measured 17 by 12 by 7 cm. It was oval, with a delicate, translucent, grayish-white capsule in which blood vessels radiating from the kidney were clearly visible. The renal capsule covered the cyst and could be stripped easily. The base by which the cyst was attached to the kidney measured about 7 by 4 cm, and the kidney itself, 12 by 7 by 6 cm. The kidney showed two deep retractions on the surface and was somewhat curved toward the anterior abdominal wall. The inside of the cyst was smooth and glistening and showed several low trabeculae, which crossed each other in irregular fashion. There was no connection with the renal pelvis. The cyst contained a clear, serous, somewhat yellowish fluid. The chemical analysis showed albumin, sugar, 20 mg per hundred cubic centimeters, non-protein nitrogen, 25.8 mg, uric acid, 2.3 mg, urea nitrogen, 7.4 mg, creatinine, 1.1 mg, and no cholesterol. The sediment showed only amorphous crystals.

The small cyst the size of a hazelnut in the cortex of the right kidney was located at the middle of the outer curvature and contained a clear, watery fluid.

The microscopic examination of the wall revealed atrophic kidney tissue on the outside and a vascular, loose connective tissue on the inside of the cyst. An epithelial lining was absent. There was no elastic tissue in the cystic wall. Examination of the kidney at the region of the deep retraction showed a disturbance in the regular arrangement of the tubuli and glomeruli. There was no increase of the interstitial fibrous tissue nor any evidence of a chronic inflammatory process in these areas.

#### SUMMARY

A case of solitary serous cyst of the kidney, which remained clinically latent during life, is reported. The presence of structural irregularities in the kidney seems to indicate that developmental disturbances are responsible for the origin of solitary serous cysts.

Trabeculation is sometimes observed covering the whole or parts of the inner surface. Multilocular cysts are occasionally seen. The contents usually consist of a clear, yellow, thin fluid which is strongly albuminous and contains urea, uric acid, chlorides and infrequently also cholesterol and fat. Contents of a bloody character are due to a secondary hemorrhage (Laquiere found this in one tenth of the cases). Secondary infection may result in a purulent fluid. Besides crystals, the sediment may contain desquamated epithelial cells from the lining of the cyst. Communications of the lumen of the cyst with the renal pelvis or the calices do not exist.

#### MICROSCOPIC APPEARANCE

The wall in general consists of three layers. The outer layer is formed by either the fibrous renal capsule or by atrophic renal tissue, the middle layer is a loose, vascular connective tissue, and the inner layer consists of cells ranging in shape from flat ones to cuboidal epithelial ones. In the majority of the cases, the epithelial lining was absent. The middle layer does not contain any elastic tissue except that found in the vascular walls. In a recent publication, Judd and Simon<sup>4</sup> stressed this fact, they contended that solitary cysts with hemorrhagic contents are not always solitary serous cysts with secondary hemorrhage into the lumen, but that they are partly primary formations originating from aneurysms, as they contain elastic tissue in their wall.

#### ETIOLOGY

There are several theories concerning the etiology of these cysts. The retention theory supported by Virchow<sup>1</sup> contends that the solitary cysts result from a constriction of tubules by scar tissue or blocking of the lumina by desquamated and degenerated tubular epithelium and contributory small hemorrhages. The absence of chronic inflammatory changes in many of the cases reported does not favor this theory. In another theory, a failure of the union between glomeruli and tubuli during the embryonal development is considered as the causative mechanism of the cysts. Boist,<sup>2</sup> on the other hand, regarded the cysts as the result of independent new formations which arise from embryonal rests. In support of this theory, which is not accepted by Lubarsch,<sup>2</sup> Ruckert<sup>2</sup> reported the existence of transitions between solitary cysts and polycystic kidneys. Sonntag<sup>2</sup> expressed the belief that they may originate from primary solid tumors due to extensive central necrosis. A new view is brought into the discussion by the investigations of Kampmeier.<sup>5</sup> In the study of fetal kidneys, he observed that during

4 Judd and Simon. Hemorrhagic Cysts of the Kidney, Surg Gynec Obst 45 601 1927

5 Kampmeier. A Hitherto Unrecognized Mode of Origin of Congenital Renal Cyst Surg Gynec Obst 36 208, 1923



Kern and Gold,<sup>1</sup> Lorentz<sup>2</sup> and more recently Spring<sup>3</sup> reported the frequent finding of fat in the liver in cases of tuberculosis. Of ninety-one cases mentioned in Spring's paper, fourteen showed complete infiltration of the liver by fat. In sixteen cases, the infiltration by fat was almost complete, and in thirty-one cases fat was found in an area corresponding to about one third of the lobule. Fifteen cases showed fat only in the periphery of the lobule, while another fifteen cases showed only traces of fat.

Table 1 gives the sex, age, color and external appearance of the patients. It shows in how many cases the liver was the seat of a passive hyperemia, of an increase in connective tissue, of infiltration by fat and of tubercles. It states whether or not ulcerative lesions were present in the intestines, and mentions the conditions in the lungs. It gives, further, the largest diameter of the islets of Langerhans in the pancreas.

Three of the 100 cases showed complete infiltration of the liver by fat. In four, the liver showed fat only in an area extending about half-way from the peripoital spaces toward the central vein, in twelve, fat was found in the outer third of the lobules, and in fifteen, fat was present only in the liver cells surrounding the peripoital spaces. Thirty-four per cent of the cases had some fat in the liver, only 3 per cent showed complete infiltration by fat. Sixty-six cases presented no fat. In addition to the 100 cases which were examined in detail with the special purposes of this study in mind, the available microscopic sections of the liver and the records of the autopsies in 767 other cases of chronic tuberculosis were examined for infiltration of the liver by fat. In 129 of these 767 cases fat was seen grossly and microscopically, while in twenty-three fat could be detected only microscopically, in other words, only 26.32 per cent of 767 cases showed the presence of fat. No attempt was made to determine the degree of infiltration by fat in this series of cases.

As table 1 further indicates, the age of the patient, the sex and the color apparently have no influence on the presence or absence of fat in the liver. There is no relationship between the external appearance of the body and the fat content of the liver.

In twenty-seven cases, a more or less severe passive hyperemia was present in the liver microscopically. None of these cases showed fat in the liver.

It is surprising that the infiltration of the liver by fat in this material was much less frequent than is described in the literature. The Amer-

1 Kern, W., and Gold, E. Ueber die Beziehung von Leberzirrhose zur Tuberkulose, *Virchows Arch f path Anat* **222** 78, 1916.

2 Lorentz, F. H. Die Leber in ihrem Verhalten zur Tuberkulose und Cirrhose, *Ztschr f Tuberk* **20** 232, 1913.

3 Spring, K. Die Leber bei Tuberkulose, *Frankfurt Ztschr f Path* **32** 32, 1925.

# CHANGES IN THE LIVER AND IN THE PANCREAS IN CHRONIC PULMONARY TUBERCULOSIS

WITH SPECIAL REFERENCE TO THE ISLETS OF LANGERHANS \*

OTTO SAPHIR, M D

CLEVELAND

It is well known that certain morphologic changes occur in the liver in cases of chronic tuberculosis of the lung. Aside from the frequent finding of tubercles, infiltration by fat and an increase in connective tissue in the liver often seem to accompany tuberculosis of the lung. The pancreas in these cases rarely shows tubercles, and only infrequently an increase in connective tissue. The correlation between the changes in the pancreas and those in the liver in cases of chronic tuberculosis of the lung, however, has received but little attention.

The study here presented deals with the examination of the liver and the pancreas in 100 cases of chronic ulcerative tuberculosis of the lung and with the data taken from 767 cases of tuberculosis. Attention was directed to infiltration of the liver by fat, the interstitial tissue of the liver and pancreas and especially to the islets of Langerhans. Other changes in the liver and pancreas, as parenchymatous changes, passive hyperemia and amyloidosis, were noted but are not discussed.

## MATERIAL AND METHODS

One hundred cases of chronic ulcerative tuberculosis were used for this study. The patients were inmates of the sanitarium which is part of the Cleveland City Hospital. The autopsies were performed from three to twenty-four hours after death. Blocks of the liver and of the tail, the head and the midportion of the pancreas were hardened in a diluted solution of formaldehyde, U S P (1:10) and imbedded in paraffin. Several blocks were used for frozen sections, and stained for fat with sudan III. Hematoxylin and eosin were used for routine stains. Mallory's and van Gieson's stains were applied to demonstrate connective tissue. Ziehl-Neelsen's method was applied to disclose tubercle bacilli. An attempt to count the number of islets of Langerhans was futile, therefore the diameters of the islets were measured with the aid of a filar ocular, and the longest diameters recorded.

## LIVER

*Infiltration by Fat*—The textbooks of pathology mentioned two conditions as causes of infiltration of the liver by fat, namely, chronic alcoholism and tuberculosis. Indeed, the liver in chronic tuberculosis serves as the every day example of infiltration of that organ by fat.

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\* From the Departments of Pathology of Western Reserve University Medical School and Cleveland City Hospital.

TABLE 1—Summary of Observations in One Hundred Cases of Tuberculosis of the Lungs—Continued

Case	Sex	Age	Color	State of Nourishment	Liver				Tuberculous Ulcers of Intestines	Largest Diameter of Islets of Langerhans, Microns
					Passive Hyperemia	Connective Tissue	Portion Infiltrated by Fat	Tubercles		
65	F	20	B	Poor	Absent	Absent	$\frac{1}{2}$	Present	Present	185
66	M	32	B	Poor	Absent	Absent	Absent	Present	Absent	330
67	M	30	B	Poor	Absent	Increase	Absent	Present	Present	285
68	F	31	B	Good	Absent	Absent	Absent	Absent	Present	495
69	F	36	W	Good	Present	Increase	Absent	Present	Present	225
70	M	30	W	Good	Present	Increase	Absent	Present	Present	330
71	F	27	W	Poor	Absent	Increase	Absent	Present	Present	520
72	M	75	W	Good	Absent	Increase	Absent	Present	Absent	365
73	M	22	W	Good	Present	Increase	Absent	Present	Present	380
74	M	48	B	Good	Absent	Increase	Absent	Absent	Absent	285
75	M	37	W	Poor	Absent	Increase	Absent	Absent	Present	385
76	M	29	W	Good	Absent	Increase	$\frac{1}{2}$	Present	Present	300
77	F	45	W	Fair	Absent	Increase	Absent	Present	Present	375
78	M	56	W	Good	Absent	Absent	Absent	Present	Present	225
79	M	36	B	Good	Present	Increase	Absent	Present	Present	315
80	M	43	W	Good	Present	Increase	Absent	Present	Present	375
81	M	43	B	Good	Present	Increase	Absent	Present	Present	345
82	M	50	B	Good	Absent	Sclerosis	Absent	Absent	Absent	400
83	M	35	W	Good	Absent	Increase	Absent	Present	Present	300
84	F	32	W	Good	Absent	Absent	Periportal spaces	Present	Present	285
85	M	46	W	Good	Absent	Absent	Absent	Present	Present	330
86	M	40	W	Good	Absent	Increase	Absent	Present	Present	307
87	M	73	W	Good	Absent	Increase	Absent	Present	Present	388
88	M	35	W	Good	Present	Increase	Absent	Present	Present	386
89	M	43	B	Good	Present	Increase	Absent	Present	Absent	315
90	M	37	B	Poor	Absent	Increase	Absent	Present	Present	300
91	F	31	B	Good	Absent	Increase	Absent	Present	Present	511
92	F	32	W	Poor	Absent	Increase	Absent	Present	Present	300
93	F	20	B	Good	Present	Increase	Absent	Present	Present	315
94	M	20	B	Good	Absent	Absent	Absent	Present	Present	367
95	F	24	W	Fair	Absent	Absent	$\frac{1}{2}$	Absent	Absent	215
96	M	32	W	Good	Present	Increase	Absent	Absent	Present	450
97	F	18	W	Fair	Absent	Absent	Periportal spaces	Present	Present	270
98	F	39	B	Good	Absent	Absent	Periportal spaces	Present	Present	300
99	M	40	W	Good	Absent	Absent	Periportal spaces	Absent	Absent	300
100	M	37	W	Good	Absent	Sclerosis	Absent	Absent	Present	315

ican literature contains few references to this subject, most of the investigations having been made in Europe. Lavenson and Karsner,<sup>4</sup> whose material was taken largely from the Philadelphia General Hospital, described the liver of tuberculous persons with special reference to periportal fibrosis. These authors gave a short description of their general observations of these livers. They mentioned only six of fifty as showing the presence of fat, and in only two of these was the infiltration by fat complete. These observations correspond with my results. The climate and diet may have some bearing on the presence or absence of fat in the liver, and this may account, in part, at least, for the difference in the observations of European and American investigators.

It may be mentioned in this connection that Begtrup<sup>5</sup> (Denmark) stated that previous to 1916, an infiltration of the liver by fat was found in from 18 to 23.5 per cent of all cases in which autopsies were performed,

4 Lavenson, R. S., and Karsner, H. T. Periportal Fibrosis of the Liver in Tuberculosis, Univ. Penn. M. Bull. **22**: 167, 1909-1910.

5 Begtrup, E. Fat Infiltration of Liver, Ugeskr. f. Læger **82**: 1199, 1920, abstr., J. A. M. A. **75**: 1686 (Dec. 11) 1920.

TABLE 1—*Summary of Observations in One Hundred Cases of Tuberculosis of the Lungs*

Case	Sex	Age	Color	State of Nourishment	Liver			Tubercles	Tuberculous Ulcers of Intestines	Largest Diameter of Islets of Pancreas Microns
					Passive Hyperemia	Connective Tissue	Portion Infiltrated by Fat			
1	F	37	B	Fair	Absent	Increase	$\frac{1}{4}$ *	Absent	Absent	300
2	F	27	W	Good	Absent	Increase	$\frac{1}{4}$	Present	Present	300
3	M	54	W	Fair	Present	Increase	Absent	Present	Absent	330
4	F	22	W	Good	Absent	Increase	Absent	Present	Present	300
5	M	39	W	Good	Present	Absent	Absent	Absent	Absent	380
6	M	58	W	Good	Present	Sclerosis	Absent	Present	Present	210
7	M	41	W	Good	Absent	Increase	Periportal spaces	Present	Absent	235
8	M	49	W	Good	Present	Absent	Absent	Present	Present	384
9	M	23	W	Good	Absent	Absent	Periportal spaces	Present	Present	228
10	M	39	W	Good	Absent	Increase	Periportal spaces	Present	Absent	265
11	M	38	W	Good	Absent	Increase	Periportal spaces	Present	Absent	295
12	M	31	B	Good	Absent	Increase	Absent	Absent	Absent	300
13	F	25	W	Good	Absent	Absent	Complete	Absent	Present	275
14	M	35	W	Good	Absent	Absent	Absent	Absent	Present	300
15	F	27	W	Good	Absent	Absent	Absent	Present	Absent	225
16	M	38	B	Good	Absent	Absent	Absent	Present	Present	360
17	M	50	W	Good	Absent	Increase	Periportal spaces	Present	Absent	270
18	F	32	B	Poor	Absent	Absent	Absent	Present	Present	365
19	M	20	B	Poor	Present	Increase	Absent	Present	Present	300
20	M	34	W	Fair	Present	Increase	Absent	Present	Absent	300
21	M	27	W	Fair	Absent	Absent	Complete	Present	Present	210
22	F	41	W	Good	Absent	Increase	$\frac{1}{4}$	Present	Present	180
23	F	29	B	Fair	Absent	Increase	$\frac{1}{4}$	Absent	Present	300
24	M	36	W	Good	Absent	Increase	Absent	Present	Present	435
25	M	54	W	Good	Present	Increase	Absent	Present	Absent	396
26	F	33	B	Good	Absent	Increase	Absent	Present	Present	435
27	M	20	B	Good	Present	Increase	Absent	Absent	Present	180
28	F	22	B	Good	Absent	Absent	$\frac{1}{2}$ †	Present	Present	165
29	M	23	B	Good	Absent	Absent	Absent	Absent	Absent	435
30	F	39	W	Good	Absent	Increase	Periportal spaces	Present	Present	195
31	M	48	B	Good	Absent	Increase	Absent	Present	Present	415
32	F	30	B	Good	Absent	Increase	$\frac{1}{4}$	Present	Present	345
33	M	46	W	Good	Absent	Increase	$\frac{1}{4}$	Present	Absent	235
34	F	25	B	Fair	Absent	Increase	$\frac{1}{4}$	Absent	Present	300
35	M	34	B	Good	Present	Absent	Absent	Present	Absent	265
36	M	60	W	Poor	Present	Absent	Absent	Present	Absent	270
37	F	20	W	Fair	Absent	Absent	Absent	Present	Present	270
38	M	34	W	Good	Absent	Increase	Periportal spaces	Absent	Absent	300
39	F	65	W	Poor	Absent	Sclerosis	Absent	Present	Absent	270
40	F	32	B	Poor	Absent	Absent	Absent	Present	Present	300
41	M	40	B	Good	Present	Increase	Absent	Present	Absent	270
42	M	21	B	Fair	Absent	Increase	Complete	Present	Absent	270
43	M	74	W	Fair	Absent	Absent	$\frac{1}{4}$	Present	Absent	300
44	M	24	B	Good	Present	Absent	Absent	Present	Absent	275
45	F	60	B	Good	Absent	Increase	Periportal spaces	Present	Present	315
46	M	21	W	Poor	Absent	Increase	Absent	Present	Present	210
47	M	40	B	Fair	Absent	Absent	Periportal spaces	Present	Present	300
48	F	35	B	Poor	Absent	Absent	Periportal spaces	Present	Present	300
49	M	57	W	Good	Absent	Absent	Absent	Absent	Absent	230
50	F	16	B	Fair	Absent	Increase	Absent	Present	Present	330
51	F	30	W	Poor	Absent	Increase	$\frac{1}{2}$	Present	Present	165
52	M	36	W	Fair	Present	Increase	Absent	Present	Present	295
53	M	25	B	Good	Absent	Absent	Periportal spaces	Present	Present	270
54	F	29	W	Fair	Absent	Increase	$\frac{1}{2}$	Present	Present	270
55	M	54	W	Poor	Absent	Increase	Absent	Present	Absent	300
56	M	40	W	Good	Present	Increase	Absent	Present	Absent	300
57	M	15	W	Good	Present	Increase	Absent	Present	Present	315
58	M	47	W	Fair	Absent	Increase	$\frac{1}{4}$	Present	Present	180
59	M	24	W	Good	Absent	Increase	Absent	Present	Absent	315
60	M	32	W	Fair	Absent	Increase	Absent	Absent	Present	300
61	F	20	B	Poor	Absent	Increase	Absent	Present	Absent	450
62	M	46	B	Good	Present	Increase	Absent	Present	Present	285
63	M	33	B	Poor	Present	Increase	Absent	Present	Present	285
64	F	17	B	Fair	Absent	Absent	$\frac{1}{2}$	Present	Present	300

\*  $\frac{1}{4}$  of the liver lobule

†  $\frac{1}{2}$  of the liver lobule

agreed that there is, as a manifestation of tuberculosis, an increase of varying degree in the fibrous elements of Glisson's capsule, they still disagreed as to whether cirrhosis of the liver is on a tuberculous basis. While MacCallum<sup>11</sup> classified tuberculous cirrhosis as a special group, Epplen<sup>12</sup> did not mention tuberculosis as an etiologic factor in cirrhosis of the liver. Lavenson and Karsner<sup>4</sup> emphasized that tuberculosis is one of the factors leading to a proliferation of connective tissue, and that these observations harmonize with the view held by some observers that tuberculosis is a frequent cause of cirrhosis of the liver. Two of their fifty cases showed cirrhosis of the liver. Schoenberg<sup>13</sup> held that tuberculous cirrhosis of the liver is a frequent observation, while Kitch,<sup>10</sup> and Kern and Gold<sup>1</sup> thought it rare. Kaufmann<sup>14</sup> was of the opinion that the changes in the liver due to tuberculosis may, in some cases, be similar to those found in Laennec's cirrhosis. Lorentz<sup>2</sup> found among 100 cases of cirrhosis, sixteen which should be interpreted as tuberculous in origin. Of 120 patients with cirrhosis of the liver studied by Blumenau,<sup>15</sup> 10.31 per cent died of tuberculosis. Merklen<sup>16</sup> and his co-workers found many tubercles in their case of cirrhosis of the liver. Spring,<sup>3</sup> however, did not believe that a true Laennec's cirrhosis is ever caused by tuberculosis. Huebschmann<sup>17</sup> recently stated that a combination of cirrhosis of the liver and tuberculosis is rare.

Sixty-seven cases of my series showed a proliferation of connective tissue. In only twenty-two cases was the increase confined to the periportal spaces. Forty-three showed an extension into the interlobular space, four of which showed a complete encircling of the lobule. The newly formed fibers of connective tissue were rich in nuclei. All the cases of fibrosis showed an infiltration mainly by lymphocytes, with a few polymorphonuclear leukocytes and endothelial cells. In the four more advanced cases there was a slight proliferation of young bile ducts, partly with and partly without lumina, and a new formation of blood capillaries. These cases also showed a slight regeneration of liver cells, and even a new formation of liver lobules. In short, the liver in these

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11 MacCallum, W. G. *A Textbook of Pathology*, Philadelphia, W. B. Saunders Company, 1924.

12 Epplen, F. *The Pathology of Cirrhosis of the Liver*, *Arch. Int. Med.* **29**: 482 (April) 1922.

13 Schoenberg, S. *Lebercirrhose und Tuberkulose*, *Beitr. z. path. Anat. u. allg. Path.* **59**: 601, 1914.

14 Kaufmann, E. *Lehrbuch der speziellen pathologischen Anatomie*, Berlin, 1922.

15 Blumenau, E. *Ueber Todesursache bei Lebercirrhose*, *Arch. f. Verdauungskr.* **18**: 1, 1921.

16 Merklen, P., Turpin, and Dubois-Roquebert. *Un cas de cirrhose tuberculeuse hypertrophique*, *Bull. et mem. Soc. med. d. hop. de Paris* **45**: 1380, 1921.

17 Huebschmann, P. *Pathologische Anatomie der Tuberkulose*, Berlin, Julius Springer, 1928.

but after this time in only from 4.5 to 6.2 per cent. This suggests that the reduced food value during the later years of the World War influenced to a certain degree, at least, the fat content of the liver. In cases of tuberculosis, the type of foods, too, therefore, should be taken into consideration in discussing the cause of infiltration of the liver by fat.

The cause of infiltration of the liver by fat is not known. Various theories are offered to explain the presence of fat in the liver, but none is convincing. Probably the latest communication on this subject is an article by Clauberig,<sup>6</sup> who believed that a lipolytic insufficiency in the liver is a necessary factor in causing the infiltration by fat. After referring to the changes in the pancreas, I shall return to this subject.

*Tubercles of the Liver*—Tubercles were found in the liver in eighty of the 100 cases. Since it is practically impossible to examine the entire liver histologically, it may be stated that in at least 80 per cent of the cases examined, tubercles were found in the liver. Lorentz<sup>2</sup> found tubercles in the liver in 99 per cent of his cases, Simmonds<sup>7</sup> in 82 per cent and Torry<sup>8</sup> in 63 per cent, while Lavenson and Karsnei<sup>4</sup> found them in only 36 per cent. Fifty-seven of the eighty cases of tubercles of the liver in my series showed ulcerative lesions of the intestines,<sup>9</sup> while in ten cases of intestinal tuberculosis no tubercles were seen in the liver. This observation, however, as mentioned before, must be taken cautiously, because of the possibility of overlooking tubercles of the liver. In twenty-seven cases, tubercles were seen in the liver with infiltration by fat. Two of the three livers showing complete infiltration by fat were the seat of tubercles. The tubercles in the livers that showed fat seemed to be more abundant, to attain a greater size and to show a greater tendency toward fusion by confluence, than tubercles in livers without fat. Since the tubercles were not counted and no measurements of their size were made, this observation should be confirmed.

*Connective Tissue*—Increase in connective tissue in the liver, periportal fibrosis and even cirrhosis have often been described as associated with ulcerative tuberculosis. Lavenson and Karsnei,<sup>4</sup> Kirch<sup>10</sup> and Spring<sup>3</sup> reviewed the literature in detail. While most of the authors

6 Clauberig, K. W. Weitere Mitteilung zum Problem der Fettleber bei Lungenschwindsucht, *Virchows Arch f path Anat* **262** 74, 1926.

7 Simmonds, M. Beiträge zur Statistik und Anatomie der Tuberkulose, *Deutsches Arch f klin Med* **27** 448, 1880.

8 Torry, R. G. The Occurrence of Miliary Tuberculosis of the Liver in the Course of Pulmonary Tuberculosis, *Am J M Sc* **151** 549, 1916.

9 This diagnosis was made grossly.

10 Kirch, E. Ueber tuberkulöse Leberzirrhose, tuberkulöse Schrumpfleber und analoge Folgeerscheinungen granulierender tuberkulöser Entzündungen in Pankreas und Mundspeicheldrüsen, *Virchows Arch f path Anat* **225** 129, 1918.

bile ducts, however, was found independent of the formation of the tubercles. The tubercles and the tissue reaction are probably caused by two different agents. While the tubercles are caused by the tubercle bacilli, the increase in connective tissue and the proliferation of bile ducts may be caused by the toxic products of the bacilli.

#### PANCREAS

*Tubercles*—Tubercles of the pancreas are rare. The textbooks state that even though the lymph nodes around the pancreas may, to a great extent, be involved in tuberculosis, the pancreas shows no tubercles. The percentage of tuberculosis in the pancreas varies. Kudrewetzky<sup>21</sup> reported tubercles in the pancreas in 9.37 per cent of his 129 cases of tuberculosis of the lungs. Van Valzah<sup>22</sup> found only one case among 200. This variation probably depends on the number of sections examined microscopically. Robinovitch<sup>23</sup> and his co-workers believed that lipase, or steapsin, and to some extent insulin, may be responsible for the apparent resistance of the pancreas to the formation of tubercles. In my series of 100 cases I encountered tubercles in the pancreas four times, but in none of my cases did I observe an extension of tuberculous lymph nodes into the pancreas, even though in five cases the neighboring nodes were filled with caseous material.

*Connective Tissue*—Increase in connective tissue in the pancreas in cases of chronic tuberculosis has not received much attention in the literature, even though it seems a rather frequent observation. The textbooks, too, hardly mention this. Italia<sup>24</sup> believed that while the pancreatic cells destroy the tubercle bacilli, the products of the tubercle bacilli produce an increase in connective tissue. Gilbert and Weil<sup>25</sup> found in thirteen of their twenty-five cases a so-called sclerosis of the pancreas. Opie<sup>26</sup> described two cases of advanced tuberculosis in which a chronic interstitial pancreatitis was found, but only one of these cases showed tubercles in the pancreas. In three cases with tubercles in the pancreas, no proliferation of connective tissue was observed. Lavenson

21 Kudrewetzky. Ueber Tuberkulose des Pankreas, Ztschr f Heilk, vol 13, abstr, Centralbl f allg Path u path Anat 3 1011, 1892.

22 Van Valzah, S. L. Tuberculosis of the Pancreas, Am Rev Tuberc 9 409, 1924.

23 Robinovitch, L. G., Stiles, G. W., and Payne, E. F. The Pancreas and Tuberculosis, Endocrinology 9 490, 1925.

24 Italia, F. E. Pancreas und Tuberculose, Riforma med, vol 1, p 55, abstr, Centralbl f allg Path 14 702, 1903.

25 Gilbert, A., and Weil, P. E. Étude anatomo-pathologique comparative de tuberculose du foie et du pancreas, Arch de med exper et d'anat path 14 729, 1902.

26 Opie, E. L. Cytology of Pancreas in Cowdry, E. V. Special Cytology, New York, Paul B. Hoeber, 1928.

cases seemed similar to the liver in early stages of Laennec's cirrhosis. Spring further stated that, contrary to the observations of Roque,<sup>18</sup> ascites and splenic hyperplasia, so typical of Laennec's cirrhosis, are absent in tuberculous cirrhosis. In none of my cases was there ascites or splenic hyperplasia.

Spring suggested, however, that changes in the liver which resemble Laennec's cirrhosis with less pronounced regeneration of bile ducts and liver cells, and unassociated with ascites and splenic hyperplasia, but with tuberculous etiology, should be classified under the term sclerosis of the liver. My investigation leads me to believe that the type of regeneration in these cases is not sufficiently different to warrant making of it a differential diagnostic feature. The presence or absence of ascites and splenic fibrosis seems of greater significance. But I agree that the conditions in these livers should not be classified as Laennec's cirrhosis, and the term sclerosis for this type of changes in the liver seems justified.

As stated before, eighty cases showed milary tubercles in the liver and fifty-five both proliferation of connective tissue and milary tubercles. Two of the four cases that were typical for sclerosis, however, revealed no tubercles even though many blocks were searched carefully, while the two other cases showed very young tubercles. In forty-three cases of fibrosis of the liver and two cases of sclerosis of the liver there were tuberculous ulcers in the intestines.

The cause of the proliferation of connective tissue in the liver is not known. Stoerk<sup>19</sup> stated the belief that the proliferation of connective tissue in guinea-pigs is directly referable to the localization of tubercle bacilli in the region of the capsule of Glisson. Whether or not this hypothesis is true cannot be said. Lavenson and Kaisner<sup>4</sup> stated that, in cases in which tubercles are not seen in the liver, the increase in connective tissue may be the result of the action of the products of the tubercle bacilli.

My figures indicate that there is no relationship between the proliferation of connective tissue and the presence of tubercles in the liver. If tubercles are found in "cirrhotic" livers, they may be independent of the connective tissues (Steinberg)<sup>20</sup>. As stated before, a proliferation of bile ducts was found to a slight degree only. In tuberculous guinea-pigs, however, the proliferation of bile duct is, according to Stoerk,<sup>19</sup> extremely marked. I was also impressed by the marked new formation of bile ducts in the livers of fifty guinea-pigs which were injected with material containing tubercle bacilli. This proliferation of

18 Roque, G. Des cirrhose tuberculeuses du foie, *Medicine* **2** 757, 1921.

19 Stoerk, O. Ueber experimentelle Leberzirrhose auf tuberkuloeser Basis, *Wien klin Wchnschr* **20** 847, 1011 and 1048, 1907.

20 Sternberg, C. Leber, Gallenblase und Gallenwege, Pankreas, in Aschoff *Pathologische Anatomie*, Jena, Gustav Fischer, 1919.



rhosis of the liver is not uncommon, yet pancreatic cirrhosis is a rare observation. Nine of my 100 cases showed an increase in connective tissue in the pancreas, while two showed the pancreas to be the seat of a marked new formation of connective tissue combined with some manifestations of regeneration. According to Scholtz,<sup>27</sup> these two cases should be called cirrhosis of the pancreas. Similar changes were encountered in the liver, but, as was brought forward in the discussion of fibrosis of the liver one is not dealing in such a case with a true cirrhosis of the liver, but with a condition that was called sclerosis. The amount of newly formed connective tissue in the pancreas in these two cases was great, but the relatively small amount of regeneration made the term sclerosis of the pancreas seem more appropriate than cirrhosis.

Table 2 is presented to show the changes in the liver in the cases of

TABLE 2—Summary of Observations in Cases of Fibrosis of the Pancreas

Case	Age	Liver			Pancreas			Tuberculous Ulcers of Intestines
		Con- nec- tive Tissue	Portion Infiltrated by Fat	Tubercles	Fibrosis	Sclerosis	Tubercles	
2	27	Increase	$\frac{1}{2}$ *	Present	Present		Absent	Present
23	29	Increase	$\frac{1}{2}$	Absent	Present		Absent	Present
31	48	Increase	Absent	Present	Present		Absent	Present
32	30	Increase	$\frac{1}{2}$	Present	Present		Absent	Present
45	60	Increase	Periportal spaces	Present		Present	Present	Present
33	46	Increase	$\frac{1}{2}$	Present	Present		Absent	Absent
47	40	Absent	Periportal spaces	Present	Present		Absent	Present
50	16	Increase	Absent	Present	Present		Absent	Present
55	54	Increase	Absent	Present	Present		Absent	Absent
95	24	Absent	$\frac{1}{2}$	Absent		Present	Absent	Absent
100	37	Sclerosis	Absent	Absent	Present		Absent	Present

\*  $\frac{1}{2}$  of the liver lobule

fibrosis of the pancreas. It further gives the age of the patient, and states whether or not tuberculous lesions were found in the pancreas and intestines.

There is no relation between fibrosis or sclerosis of the liver and the pancreas in these cases, or between the age of the patient and the fibrotic changes in the pancreas. Otherwise these observations do not justify further conclusions.

*Islets of Langerhans*—Before this study was undertaken, it was observed in routine examinations of the pancreas in cases of tuberculosis that the islets were much larger in some cases than in others. In the course of the histologic investigation, therefore, special attention was given to the size of the islets. No microscopic changes in the islets were noted in my cases. The cells appeared uniform in size and were sharply defined. No cellular infiltration and no degeneration could be made out.

and Karsner<sup>4</sup> mentioned fibrosis of the pancreas as occurring in two cases, and chronic interstitial pancreatitis as occurring in nine in their series of fifty cases of tuberculosis. Van Valzah<sup>22</sup> was of the opinion that tuberculous or toxic sclerosis of the pancreas in cases of tuberculosis is a rather frequent occurrence, but is not characteristic of tuberculosis. Scholtz,<sup>27</sup> however, did not mention tuberculosis as of etiologic moment in cirrhosis of the pancreas. Kirch<sup>10</sup> believed that tuberculosis may produce a productive chronic inflammation of the pancreas which, theoretically, at least, could precede cirrhotic changes, similar to those found in the salivary glands. In his opinion, these changes are analogous to the observations in the livers of tuberculous patients.

In none of my cases could the diagnosis of fibrosis of the pancreas be made grossly. Histologically, the diagnosis was based on the finding of an increase in connective tissue in the interlobular spaces. The connective tissue surrounding the ducts was not used as a criterion of increase. Eleven cases of my series of 100 showed a definite proliferation of connective tissue. In nine of these cases, the connective tissue extended only to a varying degree between the lobules, but did not encircle the lobules and showed no intra-acinar proliferation. Between the fibers of connective tissue, a few lymphocytes and endothelial cells were demonstrable. None of these nine cases showed tubercles in the pancreas. The remaining two offered a marked new formation of connective tissue encircling the lobules entirely. In some instances, the connective tissue extended between the acini and separated individual cells. Some of the acini were extremely small and consisted of cells with deeply stained nuclei. There was a slight new formation of ductules present, which in some sections were seen as islets in the midst of connective tissue. The connective tissue was infiltrated by a varying number of lymphocytes and endothelial cells. The islets of Langerhans seemed to be spared by the fibrotic process. Some of the sections showed as many as eight islets in a field. This observation may be explained by the retraction of the surrounding connective tissue, drawing the islets closer together. Only one of these two cases showed, in addition, tubercles, but these tubercles were not surrounded by connective tissue, and no relation between the tubercles and the proliferation of connective tissue could be made out. It may be especially emphasized that none of the cases was the seat of obstruction of the pancreatic duct.

Scholtz<sup>27</sup> called sclerosis of the pancreas combined with regeneration, cirrhosis of the pancreas. While, in his opinion, in accord with Poggenpohl,<sup>28</sup> some increase in connective tissue of the pancreas in cases of cir-

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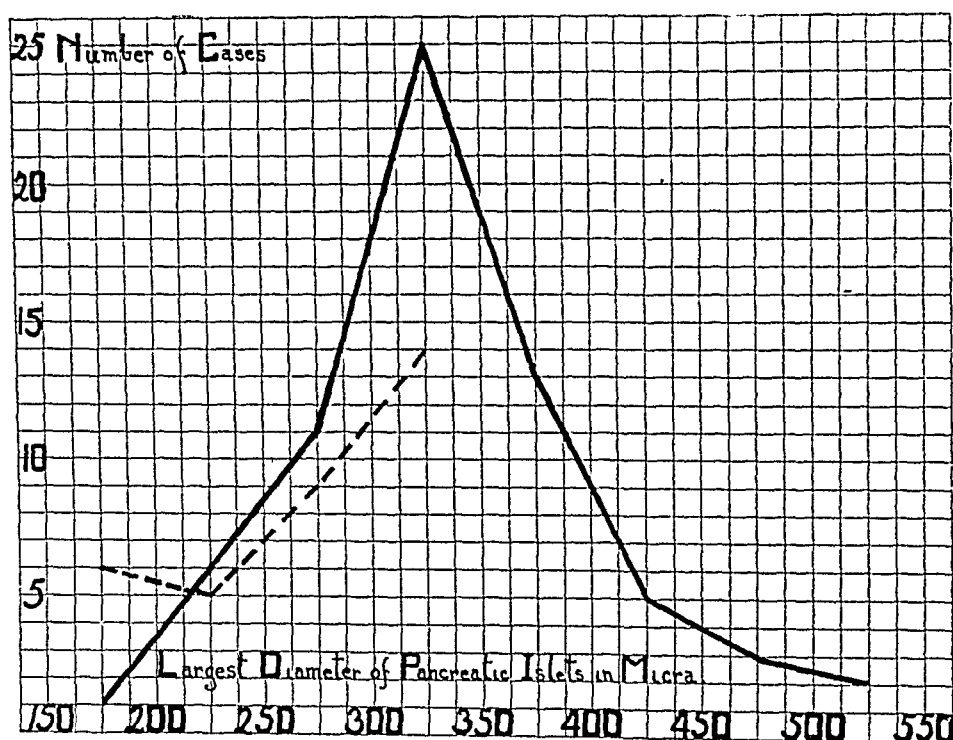
27 Scholtz, D. Beitrage zur Pankreaspathologie, Virchows Arch f path Anat **247** 467, 1923

28 Poggenpohl, S. M. Zur Frage der Veraenderungen des Pankreas in Lebercirrhose, Virchows Arch f path Anat **196** 466, 1909

measured with a filar ocular, and the largest diameter of each case recorded. An attempt to measure the smallest diameter was given up because of the great variation at the levels in which the islets were cut. Small diameters may mean not really small diameters of the islets but diameters of segments of the islets. If the diameters are large, however, it follows that the islets are large.

TABLE 3—*Largest Diameters of Islets of Langerhans in Relation to Presence and Absence of Fat in the Liver*

Measurement of Islets, Microns	Fat in Liver Present, Number of Cases	Fat in Liver Absent, Number of Cases
150-199	0	1
200-249	5	6
250-299	9	11
300-349	11	25
350-399		13
400-449		5
450-499		3
500-549		2



Graph of incidence of fat in liver, and size of pancreatic islets. Continuous line indicates cases without fat in liver. Interrupted line indicates cases with fat in liver.

The largest diameters of the islets in my cases varied from 155 to 511 microns. In comparing the slides of the pancreases with those of the livers, it was noted that cases with fat in the liver showed smaller islets than those without fat. Table 3 summarizes the numbers and measurements of the islets of cases with and without fat in the liver. The accompanying chart shows these figures graphically.

*Size of Islets*—The size of the islets in the normal pancreas varies greatly. Laguess<sup>29</sup> classified the islets according to their size. He differentiated very small islets (less than 100 microns in diameter), small (from 100 to 150 microns), medium (from 150 to 200), large (over 200) and giant islets (over 400). He believed that giant islets were exceedingly rare. The largest diameters of the islets recorded in five cases by Dewitt<sup>30</sup> were 380, 350, 330, 325 and 320 microns. MacCallum<sup>31</sup> found the normal average diameter to be 157 by 146 microns. Among ninety cases of diabetes, Cecil<sup>32</sup> found 38 per cent with islets measuring 400 microns in diameter, or more, but he believed that these islets were hypertrophied. Heiberg<sup>33</sup> held that the largest diameters of the islets varied from 225 to 275 microns. In cases of diabetes, he found hypertrophic islets measuring 400 microns in diameter. Gray and Feemster<sup>34</sup> gave the largest diameter in a new-born child as 206 microns. In a child born from a diabetic mother, they observed hypertrophic islets, the largest of which measured 728 by 324 microns. Dubreuil and Anderodias<sup>35</sup> described a similar case with the largest islet measuring 394 by 335 microns. Wright<sup>36</sup> called diameters of from 250 to 300 microns the normal limit, however, he gave the largest diameters as 411, 465, 520 and 602 microns. But islets of all his cases showed hyaline degenerative changes.

I readily recognize the difficulties in establishing the normal sizes or diameters of the islets. As long as the whole pancreas is not examined histologically and every one of the islets in the section is measured, no exact statements can be made as to the size of the islets. According to the figures mentioned, however, it is fairly safe to assume that the average largest diameter of normal islets in man measures around 300 microns.

As mentioned previously, the diameters of a number of islets from the region of the head, midportion and tail of the pancreas were

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29 Laguess, E. *Compt rend Soc de biol* **9** 402, 1893, **10** 667, 1894, cited by Cecil (footnote 32).

30 Dewitt, L. M. *Morphology and Physiology of Areas of Langerhans in Some Vertebrates*, *J Exper Med* **8** 193, 1906.

31 MacCallum, W. G. *Hypertrophy of the Islands of Langerhaus in Diabetes Mellitus*, *Am J M Sc* **133** 432, 1907.

32 Cecil, R. L. *A Study of the Pathological Anatomy of the Pancreas in Ninety Cases of Diabetes Mellitus*, *J Exper Med* **11** 266, 1909.

33 Heiberg, K. A. *Studien ueber die pathologisch anatomische Grundlage des Diabetes Mellitus*, *Virchows Arch f path Anat* **204** 175, 1911.

34 Gray, S. H., and Feemster, L. C. *Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child Born from a Diabetic Mother*, *Arch Path* **1** 348 (March) 1926.

35 Dubreuil, G., and Anderodias. *Illots de Langerhans geants chez un nouveau né, issue de mere glycosurique*, *Compt rend Soc de biol* **72** 1490, 1920.

36 Wright, A. W. *Hyaline Degeneration of the Islands of Langerhans in non Diabetics*, *Am J Path* **3** 461, 1927.

infiltration of the liver by fat showed islets in the pancreas not exceeding 275 microns in diameter. Thus, in some cases of chronic tuberculosis, the islets of Langerhans were larger than normal, and such cases did not show fat in the liver. The infiltration of the liver by fat in these cases may have depended on the size of the islets of Langerhans as well as on other factors.

Abraham<sup>41</sup> and Rosenberg and Wolf<sup>42</sup> found that tuberculosis may produce a lowered tolerance for insulin, leading in advanced cases to sudden hypoglycemia. It is possible that hypertrophy of the islets, in these cases, may be responsible for the sudden development of hypoglycemia.

#### SUMMARY

Among 100 cases of chronic ulcerative tuberculosis of the lung, thirty-four showed the presence of fat in the liver. Only three of these cases showed complete infiltration of the liver by fat. There was no relation between the infiltration of the liver by fat and the presence of tubercles in the liver and ulcerative tuberculous lesions in the intestines. There was no relation between age, color or sex and the infiltration of the liver by fat. Eighty of the cases showed tubercles in the liver. An increase in connective tissue was present in 67 per cent, but only four cases showed changes that were called sclerosis. The pancreas showed tubercles in 4 per cent. In eleven cases an increase in connective tissue was demonstrated. Only two cases showed sclerosis. There was no relation between the fibrotic changes in the liver and those in the pancreas, between tubercles of the pancreas and tuberculous lesions of the intestines, or between fibrotic changes of the pancreas and the age.

Special attention was given to the size of the islets of Langerhans. In cases in which fat was found in the liver, the largest diameter of the islets measured less than 350 microns. The diameters did not exceed 275 microns in cases of complete infiltration of the liver by fat. The pancreas in twenty-three cases which showed no fat in the liver had islets measuring more than 350 microns in diameter, ten of these islets measured over 400 microns. On the assumption that larger islets mean increased function, which, of course, is questionable, it was suggested that, it may depend on the size of the islets of Langerhans, together with other factors, whether or not the liver in cases of pulmonary tuberculosis contains fat. The larger islets may cause the sudden hypoglycemia found in some cases of diabetes complicated with tuberculosis during the course of treatment with insulin.

41 Abraham, A. Ueber die Lungentuberkulose der Diabetiker und ihre Behandlung mit Insulin und Synthalin, *Med Klin* **23** 720, 1927.

42 Rosenberg, M., and Wolf, G. Diabetes, Lungentuberkulose und Insulin, *Klin Wchnschr* **6** 936, 1927.

Fourteen cases with fat and twenty-five without fat in the liver showed islets measuring from 300 to 349 microns in diameter. None of the islets in cases with fat in the liver measured over 350 microns, but twenty-three cases without fat in the liver showed islets which measured more than this. "Giant" islets were found in the pancreas in ten cases without fat in the liver, and none in the pancreas in cases with fat in the liver. In my cases of complete infiltration of the liver by fat, the largest islets did not exceed 275 microns in diameter. The islets of cases showing fat in the liver in about half of the lobule did not exceed 300 microns in diameter.

The presence or absence of connective tissue or even of sclerosis of the pancreas, in my cases, seemed to have no influence on the size of the islets. Opie<sup>37</sup> believed that hypertrophy of the islets had been observed in association with lesions that destroy some of these structures in man. But it may be especially emphasized that none of my cases showed clinical signs of diabetes. Only one reference was found to hypertrophy of the islets in tuberculosis. Kasarnowskaja<sup>38</sup> stated that hypertrophy of the islets of Langerhans is found in cases of tuberculous toxemia of long duration. But he did not give any details as to the measurements of the islets, nor did he give any description of the organs in these cases.

It is, of course, questionable whether hypertrophy of the islets necessarily means an increase in function, which would result in hypoglycemia, but unfortunately an examination of the blood sugar was not made in my cases. It was interesting in this connection that of 131 patients suffering from chronic pulmonary tuberculosis, twenty, or 15.3 per cent, showed less than 80 mg of sugar per hundred cubic centimeters. Folin's method was used for the blood sugar determinations.

Macleod<sup>39</sup> showed that after pancreatectomy in dogs the liver contained excessive quantities of fat, which promptly disappeared after administration of insulin. Campbell and Macleod<sup>40</sup> maintained that insulin reduces the fat content of the liver. Assuming, then, that hypertrophy of the islets implies an increase in function, one would expect less fat in the liver in cases showing larger islets. It was shown before that the liver contained fat only in cases in which the diameter of the islets was less than 350 microns, and that three cases of complete

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37 Opie, E. L. *Disease of the Pancreas*, Philadelphia, J. B. Lippincott Company, 1903.

38 Kasarnowskaja, O. S. *Ueber die Veraenderungen im endokrinen Apparat der Bauchspeicheldruese unter dem Einfluss tuberkuloeser Toxaemia*, Beitr. z. Klin. d. Tuberk. **65**: 777, 1927.

39 Macleod, J. J. R. *Insulin*, Eleventh Internat. Physiol. Cong., July 24, 1923, *Lancet* **205**: 198, 1923.

40 Campbell, W. R., and Macleod, J. J. R. *Insulin*, *Medicine* **3**: 195, 1924.

- 13 Xylene on and off
- 14 Xylene
- 15 Mount in xylene balsam

For those who desire a more rapid method, the following is suggested, but not recommended as routine

- 1 Place small pieces of tissue in acetic methyl alcohol fixative 1 hour
- 2 Absolute methyl alcohol 1 hour
- 3 Absolute methyl alcohol 1 hour
- 4 Blot
- 5 Xylol  $\frac{1}{2}$  hour
- 6 Blot
- 7 Paraffin (56 C incubator) 1 hour
- 8 Block and cool quickly
- 9 Cut sections and stain as described

#### SUMMARY

A rapid method for preparing tissue for section without ethyl alcohol has been developed which has proved reliable. Any of the ordinary staining methods may be used following this new method of fixation.

# Laboratory Methods and Technical Notes

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## A PARAFFIN METHOD FOR SECTIONS WITHOUT ETHYL ALCOHOL

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Owing to difficulty in obtaining suitable ethyl alcohol, a routine rapid method for preparing tissues for section without ethyl alcohol has been evolved. In results, this method compares favorably with any of the longer routines. Specimens are preserved in a diluted solution of formaldehyde, U S P (1:10) until ready to dehydrate.

### FIXING

The fixative consists of absolute methyl alcohol, 6 parts, chloroform, 3 parts, and glacial acetic acid, 1 part.

The fixative must be freshly prepared. Use small, wide-mouth bottles of 50 cc capacity, and about 30 cc of fixative for each bottle. When several pieces of tissue from the same case are to be examined, use larger amounts of fixative in proportion.

- 1 Cut pieces 3 by 6 mm and place them in the fixative from  $\frac{1}{2}$  to 3 hours, according to the size of the block
- 2 Pour off the fixative and add absolute methyl alcohol 1 hour
- 3 Absolute methyl alcohol 1 hour
- 4 Blot (by placing tissue on filter paper)
- 5 Chloroform and paraffin (saturated) at 38 C 6 hours or overnight
- 6 Paraffin (56 C) 2 hours
- 7 Block and cool quickly
- 8 Cut sections from 6 to 8 microns thick
- 9 Fix sections to slides with the usual albumin fixative

### STAINING

- 1 Xylene 3 minutes
- 2 Absolute methyl alcohol 3 minutes
- 3 70 per cent methyl alcohol 3 minutes
- 4 Tap water 3 minutes
- 5 Harris hematoxylin 6 minutes
- 6 Acid alcohol (1 per cent hydrochloric acid in 70 per cent methyl alcohol) 10 seconds
- 7 Ammonia water (8 drops to tumbler of tap water, must be freshly prepared) 5 minutes
- 8 Tap water 8 minutes
- 9 Eosin ( $\frac{1}{4}$  of 1 per cent watery solution)  $\frac{1}{2}$  minute
- 10 95 per cent methyl alcohol on and off
- 11 Absolute methyl alcohol on and off
- 12 Absolute methyl alcohol on and off

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\* Submitted for publication, Feb 10, 1929

\* From the Ellis and Butler Laboratories



- Deficiency of Iodine
- Deficiency of Iron
- Deficiency of Other Minerals
- Effects of a Deficiency of Water
  - Effects on Infants
  - Effects on the Blood
  - Experimentally Produced Effects in Animals
  - Effects in Plants
- Effects of a Deficiency of Vitamins
  - Effects of a Deficiency of Vitamin A (Antixerotic)
    - Visual Apparatus
    - Respiratory Tract
    - Alimentary Tract
    - Urinary System
    - Blood
    - Reproductive Tract
    - Suprarenal Gland
    - Miscellaneous Organs
  - Effects of a Deficiency of Vitamin B (Antineuritic)
    - Nervous System
    - Musculature
    - Heart and Blood Vessels
    - Stomach and Intestines
    - Liver
    - Pancreas
    - Kidney
    - Reproductive Tract
    - Suprarenal Gland
    - Thyroid Gland, Parathyroid Glands and Hypophysis
    - Thymus and Spleen
    - Blood
    - Skeleton
  - Effects of a Deficiency of Vitamin C (Antiscorbutic)
    - Blood Vessels and Blood
    - Skeleton
    - Teeth
    - Alimentary Tract
    - Liver
    - Pancreas
    - Spleen and Thymus
    - Kidney
    - Reproductive System
    - Endocrine Organs
    - Suprarenal Glands
  - Effects of a Deficiency of Vitamin D (Antirachitic)
    - Weight and Length of the Body
    - Teeth
    - Skeleton
    - Bone Marrow
    - Blood
    - Spleen and Lymph Nodes
    - Gonads and Endocrine Organs

# General Review

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## RECENT WORK ON THE EFFECTS OF INANITION AND OF MALNUTRITION ON GROWTH AND STRUCTURE \*

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MINNAPOLIS

### Total Inanition

#### Effects on the Body in General

##### General Effects on Children, as Shown by

###### Indexes of Nutrition

###### Effects on Weight at Birth and the Ratio of the Male to the Female Sex

###### Retardation of Growth

###### Recovery

#### Effects on Vertebrates

##### Adult Animals

##### Young Animals

#### Effects on Invertebrates and Plants

### Effects on Individual Organs and Systems

#### Integument

#### Skeleton and Teeth

#### Muscular System

#### Nervous System

#### Eyes

#### Heart

#### Blood and Blood-Formation

#### Spleen and Lymph Glands

#### Thymus

#### Alimentary Canal

#### Liver

#### Pancreas

#### Submaxillary Gland

#### Kidney

#### Female Reproductive System

#### Male Reproductive System

#### Suprarenal Glands

#### Thyroid Gland

#### Parathyroid Glands

#### Hypophysis

### Partial Inanition

#### Effects of a Deficiency of Protein

##### Malnutritional Edema

##### Experiments on Animals

#### Effects of a Deficiency of Minerals

##### Deficiency of Calcium

##### Deficiency of Phosphorus

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\* Submitted for publication, July 10, 1928

~ From the Institute of Anatomy, University of Minnesota

discussed the general relation of inanition to pathology and medicine recalling the dictum of Hippocrates that hunger has "potentia sanandi, debilitandi et occidendi." He reviewed the effects of starvation on the weight, on the blood-vascular system and on the urine, together with its therapeutic applications in various diseases.

### TOTAL INANITION

Under the head of total inanition will be considered the effects of total inanition in man and lower organisms. Since the effects of subsistence on water alone are similar to those in total inanition, they will also be considered here, although, according to a strict definition, this state is a form of partial inanition.

#### EFFECTS ON THE BODY IN GENERAL

The studies of total inanition in human beings have to do almost entirely with incomplete inanition, i.e., with the effects of a general underfeeding of various grades. In conditions of malnutrition or famine in man, however, there is great variation in the extent to which the various essential factors of nutrition are deficient. This complicates the results, which are correspondingly variable and difficult of interpretation. Some of the effects of famine will therefore be discussed later under the head of partial deficiencies, such as malnutritional edema (due to a deficiency of protein), scurvy (due to a deficiency of vitamin C) and rickets (due to a deficiency of vitamin D).

Attention may be called first to several works which involve a more or less extensive review of various phases of the subject. The publications of Rossle (1923), Schlesinger (1925) and Czeiny and Keller (1925) included observations on the effects of inanition and malnutrition in children, with extensive bibliographies. Vainot (1925) summarized the previous work by himself and his associates, including that on the dissociation of ponderal and statual growth under various conditions of malnutrition. Herzenberg (1926) and Stefko (1927) reviewed the effects of the Russian famine. An unusually severe type of tuberculosis in malnourished Russian children was described by Stefko (1923). The variations in effect on the weights of organs according to the type of acute or chronic malnutrition in children were discussed by Aron and Pogorschelsky (1926). Edelmann and Savi (1922) described a characteristic syndrome with cachexia and general glandular insufficiency that may appear as a result of inanition or infections. Nearly a century ago, Howard (1839) gave an extensive account of the clinical symptoms and postmortem appearances caused by underfeeding among the industrial population of Manchester. The increased susceptibility to infections was recognized. The brain and meninges were found congested, viscera generally atrophied and anemic, blood scanty and pale,

- Effects of a Deficiency of Vitamin E (Antisterility)
  - Reproduction in the Male (Sterility)
  - Reproduction in the Female (Sterility)
  - Lactation
  - Paralysis of the Young
- Effects of a Deficiency of the Recently Discovered Vitamins
  - Antipellagra Factor (P-P), B<sub>2</sub> or Vitamin F
  - Other Vitamins (Vitamin G)

The term inanition as used here in its broader sense indicates a pathologic condition of body due to the lack of any foodstuff (including water) which is essential to the living organism. As to the character of the inanition, one may distinguish total inanition, with absence or insufficiency of all forms of nutriment, from partial inanition with the absence or insufficiency of one or more but not all of the various essential constituents of food. As to the degree of inanition, one recognizes (1) complete inanition, with entire absence of all food (as in total inanition) or of the deficient elements (as in partial inanition), and (2) incomplete inanition, with merely an insufficiency of either all food or certain essential elements.

The various types of inanition are summarized in the following tabulation:

Inanition	A Total (quantitative)	1 Complete—no food or water	<div style="display: inline-block; vertical-align: middle;">           Of one or more of the necessary foodstuffs         </div> <div style="display: inline-block; vertical-align: middle; margin-left: 10px;">           Proteins Fats Carbohydrates Salts Vitamins Water         </div>
		2 Incomplete—general underfeeding	
	B Partial (qualitative)	1 Complete (entire absence)	
		2 Incomplete (insufficient amount)	

The subject of inanition is accordingly broad in scope and includes various disorders arising from deficiencies of essential foods. Even when restricted to the morphologic phases, the bibliography to 1924 included about 2700 titles, which were reviewed in my previous work (Jackson 1925). The present survey of the more recent literature (including also a few papers previously overlooked) comprises about 730 titles, which will be classified according to the various deficiencies and the organs affected. It is hoped that a systematic review of this literature, even though necessarily somewhat brief and superficial, will be useful to numerous workers in the field of nutrition. The point of view in this survey is primarily morphologic. The physiologic and biochemical aspects are therefore mentioned only incidentally in relation to the effects on growth and structure.

The physiologic and chemical aspects of inanition are fully considered, and an extensive bibliography is furnished, in the treatises by Aron (1924) and McCollum and Simmonds (1925). Reviews of the nutritional disorders, especially from the physiologic and clinical standpoints, were contributed by Burnett (1925, 1926, 1927), Elias (1925),

in Vienna was lower during the period from 1919 to 1922 than in the subsequent two years with better nutrition, also that the monthly average reached a maximum of from 3,300 to 3,350 Gm in the summer, decreasing to a minimum of about 3,100 Gm during the winter (on account of a deficiency of vitamins) Sorokin (1925) reported a considerable decrease in Russian weight at birth, and an increase in the percentage of stillborn infants, and deaths of infants shortly after birth Slemons and Fagan (1927) somewhat doubtfully concluded that overgrowth of the fetus can be prevented by underfeeding during pregnancy

According to Bayer (1924), the Bavarian statistics show a fairly constant prewar ratio of 1,062 males to 1,000 females The first term of this ratio rose to 1,087 in 1918, decreasing again to 1,072 in 1922 He doubted whether inanition, however, was responsible for the change The consideration of effects of famine in war time on the number of births, will be included later under the head of the effects on the reproductive system (ovary)

**Retardation of Growth** The incidence of malnutrition among infants and older children as a result of the conditions of war likewise appears somewhat variable Thiele (1917), of Chemnitz, concluded that, to 1917, the health of German school children in the country districts was unimpaired by malnutrition, but that in the large cities an increasing amount of retardation in physical development was evident Bachauer (1917), of Augsburg, did not find any change for the year 1917, but for 1921 he noted a decrease in average weight and also in the range of variation Haeberlin (1918), in a review of the literature, did not find any detrimental effect of conditions due to the war on weight or length of body, girth of chest, etc., in German children Birk (1918), of Kiel, did not note any bad effects on children of preschool age, but observed the effects of malnutrition among school children Stephan (1923) did not find any significant changes in the average stature and weight of Mannheim school children on comparing the measurements for the corresponding ages in the prewar years (1912 to 1914), the war years (1916 to 1918) and the postwar years

In Vienna, however, Zappert (1920) noted among infants of the first year a marked decrease in average weight during 1916 and 1917, which reached a minimum in 1918, with a rapid increase following in 1919 Kaup (1921), of Munich, also found a decrease of from 12 to 2 per cent in the average stature and of from 32 to 5 per cent in the average weight of 1,200 "Berufsrekruten" in 1920, in comparison with the corresponding data for 1913 Davidsohn (1919, 1922), in Berlin, Jaenicke (1921), in Apolda, Vonessen (1921), in Köln, Schlesinger (1922, 1924), in Frankfurt, and Schmidt (1924), in Bonn, likewise found in school children a subnormal weight and stature, which was ascribed to previous malnutrition during the war Stefko (1925),

heart flabby, stomach and intestines empty and contracted, and the gall-bladder invariably distended with bile. None of these observations, however, was considered specific for starvation.

*General Effects on Children*—Indexes of Nutrition. There is continued dispute as to the significance of various physical indexes in the diagnosis of malnutrition in children. Many clinical observers, for example, Jaenicke (1921) and Vonessen (1921), found that Rohrer's ratio of weight to height and similar indexes of bodily build are inadequate as indications of the nutritional condition, unless supplemented by additional clinical data.

Hereditary and racial differences in build also must be considered, especially where mixed populations occur. Dublin and Gebhart (1924) found the usual American tables of heights and weights inapplicable to children of Italian parentage in New York City. Emerson and Manny (1924, 1924a), however, using the new standard tables of the National Health Council, claimed that children 7 per cent or more underweight (for height) invariably manifest other unmistakable signs of malnutrition. Similarly, Garrahan and Bettinotti (1924) concluded that Wood's tables are as reliable as any of the more complicated methods in detecting the undernourished children in Buenos Aires.

Guttmann (1925) devised a new functional test (based on the expansion of the circumferences of the elbow and the chest) which is said to agree closely with the clinical diagnosis of malnutrition, whereas the Rohrer index gives agreement in only 29.6 per cent of the cases, the Boinhardt index in 30 per cent, the Livi index in 32.5 per cent and the Brugsch index in 44.6 per cent. Tsurumi and Nakatate (1924) asserted that Pirquet's index of nutrition cannot be applied to the Japanese. Beeuwkes (1926) likewise found Pirquet's "Pelidisi" system unreliable as an index of nutrition in the Russian famine, especially in cases of rickets and hunger edema. The various physical indexes of nutrition were discussed in detail by Paton and Findlay (1926). The work of Variot and his students on the dissociation of statual and ponderal growth was confirmed by Tioncay (1923), and reviewed by Variot (1925).

*Effects on Weight at Birth and the Ratio of the Male to the Female Sex*. The data cited in my previous work (Jackson, 1925) indicated that in most cases there had not been significant decreases in weights at birth in Europe on account of the food shortage during the war. Binz (1919) added records from 8,000 births in Munich showing that changes had not appeared in the average length of body, but that a slight decrease had appeared in weight at birth and in circumference of head in 1917, compared with 1914. Bondi (1924) found in Vienna a definite decrease in the average weight at birth from 3,201 Gm. in 1913 to 3,023 Gm. in 1916. Abels (1925a) likewise showed that the average weight at birth

*Effects on Vertebrates—Adult Animals* A comprehensive review of the effects of inanition on animals was given by Lion (1924). The effects on behavior in animals were reviewed by Stone and Lindley (1928).

The question as to the effect of inanition on tumors has often been investigated, with somewhat variable and inconclusive results. Sugiyama and Benedict (1926) found that transplants of the Flexner-Jobling rat carcinoma disappeared in 73 per cent of the underfed hosts, and in only 18 per cent of the fullfed controls. However underfeeding after the engrafted cancerous tumors had been well established did not prevent subsequent growth of the tumors. The results confirmed the observations of Moersch (1909). Favorable results were also obtained by underfeeding mice that had spontaneous mammary carcinomas.

A decreased resistance to various types of infection during inanition has frequently been observed in man during famine and also in experiments on animals. Schwarz (1927) demonstrated that intravenous injections of streptococcus and staphylococcus were much more rapidly fatal in starved young mice, weakened cellular reactions to the infection were observed in the spleen and the kidney. The possible relations of a deficiency of vitamins to infection and malignant growths will be considered later.

According to Yamasaki (1923), adult mice on diets productive of total inanition live four or five days, with a loss of about 27 per cent in weight. Danforth (1927), however, found that in a peculiar, markedly obese strain of yellow mice obtained by cross-breeding, a diet of lettuce and water led to a decrease in weight from 73 Gm. to 24 Gm. (a loss of 67 per cent) in twenty-eight days, and that refeeding with a normal diet, brought about a complete recovery from a maximal loss of 69.2 per cent. Wetzel (1925) observed that the loss of weight in adult pigeons receiving water only corresponds to the autocatalytic law. The mean duration of life was  $25.2 \pm 0.9$  days. The loss of weight in thirty days was  $51.5 \pm 0.6$  per cent, reaching a maximum of 53.4 per cent in one bird that survived forty days. Dobieff (1927) noted that the dogfish (*Scyllium*) can survive a fast up to 112 days, with a loss of 33 per cent in weight.

Hayashi (1924b) found that in the rat the organs can be classified into three groups according to their several weight curves during inanition: (1) those the weights of which decrease parallel with the body weight—the pancreas and the parotid and submaxillary glands, (2) those the weights of which decrease more rapidly—the thymus, spleen and liver, and (3) those the weights of which decrease less rapidly—the kidney, ovary, testis, hypophysis, thyroid and heart. The suprarenal gland, he found, did not lose weight, often it gained weight. The detailed effects on the various individual organs will be reviewed later.

Sorokin (1925) and Newsoroff (1927) cited data similarly indicating that the Russian children still showed marked subnormality in average weight and length on account of the previous period of war and famine.

**Recovery from Effects of Malnutrition** Children show great variability in their capacity for recuperation, depending largely on the duration and character of the previous malnutrition. Bloch (1920) observed a marked increase in stature and weight among thirty malnourished girls taken from Halle to a sanatorium in Switzerland for six weeks. Schlesinger (1922, 1924) made an especially careful statistical study of the subject among school children in Frankfurt-on-the-Main. Retardation increased progressively during the war and apparently persisted thereafter. The greatest retardation in stature in most age groups occurred in 1920, the average stature being 4.3 per cent below normal. There was great improvement in 1921-1922, the average stature approaching normal in many groups, but a marked decline again in 1923. The maximal retardation in weight was reached in 1917 with a subnormality of from 4 to 12 per cent in the various groups (the greatest deficiency occurring at the age of 3 years). In the following years there was improvement with a decrease again in 1923. Rohrer's index did not always vary in correspondence with the changes in average weight. Bluhdorn and Lohmann (1922) followed thirty-eight cases of infantile malnutrition. Of these ten resulted in death, but most of the others eventuated in full recovery of the normal length and weight of body. Jenks (1926) presented data indicating that school children of Munich were still subnormal in weight and stature. Roberts (1927) concluded from repeated examinations that American children underweight or overweight tend to remain so. According to Variot (1925) the chances for recovery under proper refeeding are good in most cases, even after an extensive period of repression of growth. Stefko, on the other hand, concluded that the prolonged famine had reacted unfavorably on the general constitution of the Russian people.

Gibbon (1922), in Vienna, and Paton and Findlay (1926), in Scotland, found little evidence that malnutrition in children is caused directly by lack of nourishment. But Paterson and Marr-Geddes (1927), from a study of 100 cases, concluded that the chief cause of gastric trouble and failure to gain in weight among the outpatient infants of hospitals was underfeeding or starvation.

The extent of the endurance of total inanition in the new-born is indicated approximately by the length of life of infants born with congenital atresia of the esophagus. Sheldon (1926) reported six cases in which the duration of life ranged from six to thirteen days, averaging nine days.



in *Bursaria* and *Dileptus*, including the regeneration of amputated portions, Cleveland (1925, 1925a), the effects on several parasitic protozoa (*Trichonympha*, *Leidyopsis*, *Trichomonas*, *Stieblomastix*) during starvation of the termite host (*Termitopsis*). The remarkable reduction process exhibited by the coelenterates was described by Hadzi (1912), for *Clusaria*, and by de Beer and Huxley (1924) for *Aurelia*. The changes in *Planaria* were studied by Child (1914) and Wilhel, Hyman and Rifenburgh (1925). Dawydoff (1924) obtained complete recovery of the Nemeitean worm *Lineus lacteus* after reducing it to an embryonal state by inanition. Cardot (1924) observed abnormalities in ovulation and embryonic development caused by malnutrition in the land snail *Agriolimax agrestis*.

Several studies concerned the effects of starvation on insects especially during development. These include the experiments of Singh-Pruthi on the mealworm (*Tenebrio molitor*), of Ezikov (1922), Jezhikov (1925) and Cousin (1926) on the blow-fly, *Calliphora*, of Titschack (1926) on the clothes-moth, *Tineola*, and of Stscherbinovskij (1924) on the moth, *Malacosoma*. Some observations on starvation of adult insects were made by Fink (1925) on the potato beetle, *Leptinotarsa*, and by Abbott (1926) on the roach, *Periplaneta*.

Huxley (1921) studied the relative resistance of the various tissues in the process of dedifferentiation during starvation in the Ascidian, *Perophora*. Some further data from experiments on invertebrates will be mentioned later in connection with considerations of the various organs and also under the head of mineral deficiencies.

Two important experiments on plants may be cited. Harris (1912) made an extensive biometric study to determine whether hereditary effects are transmitted in the bean plant (*Phaseolus vulgaris*) after starvation through three generations. Only slight effects persisted after the plants returned to normal nutrition. Schaffner (1925) demonstrated that sex in the higher plants (*Arisaema*, *Cannabis*, *Thalictrum*, *Humulus*) is not predetermined, but can be experimentally modified or reversed by variation in the nutrition. Further studies on plants will be mentioned later in connection with the studies of deficiencies of water and minerals.

#### EFFECTS ON INDIVIDUAL ORGANS AND SYSTEMS

*Integument*—Differences in the relative loss of subcutaneous fat in various regions of the body during malnutrition were reviewed in my previous work (Jackson, 1925). Merkel (1890) noted that fat never disappears from the hairy scalp, even in extreme emaciation. Coerper (1924) emphasized the close relation between the bodily habitus and the amount of subcutaneous fat. The cutaneous turgor and blood supply are indexes of nutrition that are not closely related to the habitus. Ponomareff (1921), as did many other observers, reported an enormous

**Young Animals** Hartwell (1927) found that pregnant rats on a restricted diet usually showed a continued increase in weight, although the number of the young rats and their weights were distinctly decreased. The continued growth in length of body by young rats held each at constant weight by general underfeeding (as well as by feeding on diets variously deficient in part) was demonstrated by Winters, Smith and Mendel (1927). This is in agreement with the results of earlier observers demonstrating the dissociation of statual and ponderal growth during malnutrition in man and various animals. Smith and Bogin (1927) observed in underfed young rats a progressive necrosis and dry gangrene beginning at the tip of the tail and extending forward. The vascular walls appeared somewhat thickened, the cartilage cells necrotic and the muscle fibers hyalinized with pyknotic nuclei.

Some experiments have been made confirming the dissociation of growth in mass and length in frog larvae. Krizenecky (1925) observed that young tadpoles of *Rana fusca (temporaria)* sometimes continued development (formation and differentiation of the hind limbs) for a few days without food. In another experiment (1926), tadpoles up to 16 days of age were found continuing to grow in length during inanition, the skeleton being formed at the expense of other parts of the body. Groebels (1925) noted this persistent growth in length during starvation in tadpoles about 14 mm long, but noted a decrease when the starvation began in tadpoles from 16.8 to 20.5 mm long. Heitwig (1924) found that in starved frog tadpoles the central nervous system and sense organs were unusually resistant, although the lens fibers underwent liquefaction. The body musculature, the liver and especially the thymus became remarkably reduced in size. The intestine underwent a remarkable involution and a reduction in size, somewhat like the change during normal metamorphosis.

The effect of intermittent fasting on subsequent growth in tuitons was discussed by Krizenecky (1918). Podhradský and Kostomarov (1925) demonstrated a persistent growth of the skeleton and the head of carp starved at 6 weeks of age. The increase was lost again later, and did not appear in carp starved from the age of 3 months on. The increase was in flesh weight, not in dry weight. D'Ancona (1921, 1922, 1926, 1927b) made a series of studies of the eel (*Anguilla*) starved from eighty-one to 657 days with loss of from 21.1 to 61.5 per cent in weight. In young eels (1925, 1926b, 1927a), the loss in weight reached 59.6 per cent in five months.

*Effects on Invertebrates and Plants*—The effects of inanition in invertebrates and plants were discussed fully in my previous work (Jackson, 1925). The additional papers will be mentioned briefly. For the Protozoa, Vieweger (1918, 1925) studied the structural and volumetric changes in the cell body and nucleus of *Colpidium*, Sokoloff (1923), the effects

was ascribed to changes in the bone, and not merely to resorption of the soft parts. Stefko (1927a), however, concluded that the tendency is rather toward brachycephaly, especially in the young (probably caused chiefly by rickets).

Watanabe (1924) found that regeneration of the skull bone after experimental aseptic fracture was not appreciably affected by underfeeding in the guinea-pig and white rat. The effect of a deficiency of vitamins will be mentioned later.

The teeth appear to be relatively resistant to simple inanition or underfeeding. Although it is generally believed that carious teeth are frequently associated with malnutrition in children, Emerson (1925) did not find any correlation between underweight and carious teeth among 1,500 school children in Rochester. However, he stated that orthodontic treatment is not likely to be successful in malnourished children.

*Muscular System*—Degenerative changes in the muscles of starved Russian children and adults were noted by Stefko (1927a). Fetuses, during maternal starvation, also presented a general hypoplasia of the muscular system.

According to Corti and Fussi (1919), glycogen droplets disappeared from the sarcoplasm of striated muscle fibers of the hedgehog (*Eriacus europaes*) during a few days of fasting, but more slowly in hibernation. During the necrosis of the tail observed by Smith and Bogin in underfed rats, the muscle fibers showed hyalinization with nuclear pyknosis. Hertwig (1924) noted marked reduction of the body musculature in starved tadpoles of *Rana fusca*. Berg and Falk (1924) studied the fat changes in the muscle fibers of the frog (*Rana temporaria*) fasting from one to five months. Dakin and Dakin (1925) observed gradual reduction of the musculature in the goldfish during its starvation up to two months. In the striated muscle fibers of the esophagus in the eel (*Anguilla*), D'Ancona (1926a, 1927b) found the sarcolemma, myofibrillae and lines Z and M more resistant to protracted inanition, the other lines disappeared.

*Nervous System*—Anitschkoff and Sawodski (1922) interpreted the observed weakness of the various sphincters (anal, vesical and pyloric) in victims of famine as an effect of starvation on the corresponding spinal nerve centers. Beuwkes (1926) found the nervous symptoms inconstant in these cases. The nervous system is resistant to loss in weight during starvation. Stefko (1927a) gave tables for various ages showing a subnormality of from 2.5 to 14.5 per cent in the weights of the brains of starved children in comparison with the normal children of corresponding ages. For the younger ones, this probably represents chiefly retardation in growth, however, rather than actual loss in weight of the brain. In adults, the apparent loss in

increase in the incidence of furunculosis and other suppurative lesions of the skin during the Russian famine. The apparent cause was general debility and poor cutaneous circulation (due to weakened heart action). Amitschkoff and Sawodski (1922), in addition, noted a slow regeneration of wounds under such conditions. Engelking (1923) observed the occurrence of an exudative diathesis in younger malnourished children, and of a seborrheal diathesis in older malnourished children.

According to Schulmann and Marek (1927), subcutaneous bullae experimentally produced in rabbits persisted for a much longer period during starvation. Sheldon (1924) described in detail the structure of the so called "hibernating gland" in white rats as it appeared during starvation and refeeding. The changes were similar to those in ordinary adipose tissue. Moipurgo (1927) found it possible to make successful homoplastic transplants of skin in underfed rats, although such transplants invariably failed in normal rats. He believed that the failure was due to a defensive reaction of the host (like resistance to infections), which is reduced by inanition. Chang (1926) noted in underfed albino rats a retardation in the growth of hair, which was improved by thyroid feeding. Ogneff (1908) reported that the lighter color of the starved amphibian *Axolotl*, is caused by an atrophy of the dark chromatophore cells which are in part destroyed by phagocytosis. According to Svoboda (1924), the process of ecdysis (desquamation of the skin) in amphibians (*Triton*) depends on the opposing factors of keratinization and formation of nuclear chromatin in the epidermal cells. The former is favored by inanition and accelerates ecdysis, while the latter is favored by good nutrition and retards ecdysis.

*Skeleton and Teeth*—A variable degree of "Hunger osteopathie" involving osteoporosis and osteomalacia, has often been observed in persons subjected to famine or chronic underfeeding. The recent studies of this effect of malnutrition in human beings are chiefly from Russian sources. Stefko (1925a) noted a disturbance of ossification of fetuses from starved mothers. The changes are ascribed to characteristic lesions in the cartilage (chondrodystrophia foetalis ex inanitione). The osseous lesions somewhat resemble those of osteogenesis imperfecta and infantile scurvy (Barlow's disease).

Atrophy and deformities of the vertebrae were likewise found in adults by Stefko (1926, 1927) and Stefko and Schneider (1928). The result of such atrophy is a decrease in stature. Henselei (1913), confirming the earlier work of Nehring, showed a marked effect of malnutrition on the form of the head in swine. Data were cited by Iwanowsky (1923, 1925) and Baslei (1925) indicating that even the human adult cranium may become decreased in weight and size, with relative elongation (dolichocephaly), as a result of famine. The result

conclusion that neither lymphocytosis nor leukopenia is constant or characteristic, although anemia of a secondary type occurs in severe hunger edema

Much of the recent work refers to the effects of the Russian famine. Beeuwkes (1926) reported an average erythrocyte count of 4,000,000, and counts sometimes as low as 2,500,000, with poikilocytosis, he frequently found leukopenia with a decrease in polymorphonuclears, and hydiemia in 30 per cent of the cases. Stefko (1926, 1927a) concluded, from his extensive studies, that starvation, both prenatal and postnatal, has an especially severe effect on the derivatives of the mesoderm (the blood, the vascular system, the skeleton and the muscles). In Moscow, the proportion of anemic school children steadily increased from 9 per cent in 1919 to 74 per cent in 1925. During famine, the blood picture varies greatly. Stefko (1927a) recognized two groups among the children: (1) those with thickening of the blood, and (2) those with thinning of the blood (cases with edema). In the first group, the number of erythrocytes reaches 6,400,000 per cubic millimeter, with a decrease in the content of water in the blood. There is not any marked change in the total or in the differential leukocyte counts. In the second (edemic) group, the number of erythrocytes may sink to 2,500,000, with hydiemia. The leukocyte count is increased, especially the number of the lymphocytes and transitional forms, and the number of myelocytes. The modifications of the blood correspond with the changes in the blood-forming organs. The adipose bone marrow of famished adults becomes gelatinous, that of children undergoes a myeloid metamorphosis. The appearance of myelocytes and normoblasts in the liver indicates here, also, a renewal of the primitive blood-forming function. The changes in the blood and in the blood-forming apparatus during inanition were studied also by Tschelozowa.

Gage and Fish (1924) observed that in man the fatty particles (chylomicrons) that appear in the blood plasma after a meal containing fat gradually disappear within from six to ten hours. In a well nourished man, the particles reappear during the characteristic lipemia after about thirty hours of fasting. The chylomicrons are more distinct and numerous in animals with concentrated, fat-containing food (dog, cat, rat) than in those with bulky food containing little fat (cow, goat, sheep, horse, rabbit).

Suzuki (1925) studied the blood and hematopoietic tissues in guinea-pigs starved from four to thirteen days. The erythrocyte count usually increased somewhat, with early lymphopenia and later pseudo-eosinophil leukocytosis. There was, correspondingly, an atrophy of the lymphoid tissue (lymphatic follicles, splenic nodules) but increased granulopoiesis in the myeloid tissue (bone marrow, spleen and lymphoid organs). Streicher and Emmel (1925) and Emmel and other asso-

weight of the brain was 95 per cent in eight men of from 48 to 50 years, and 23 per cent in five women of from 20 to 25 years. Some brain weights were recorded also by Sedlezky (1924). The microscopic changes that were noted included atrophy and degeneration of the pyramidal cells of the cortex, with a loosening up of the white matter, especially in cases of edema. The observations of Lenz on the chemical changes in the brain were also cited. Aron, Lasch and Pogorschelsky (1925) and Aron and Pogorschelsky (1926) found that in dystrophic infants the brain weight is retarded less than the body weight, which is in accordance with the conclusions of earlier observers. Variot (1925) showed that in children the growth of the brain in general undergoes relatively slight disturbance during malnutrition.

In fasting tadpoles of *Rana fusca*, Heitwig (1924) similarly observed that reduction in the size of the central nervous system and sense organs does not follow malnutrition.

*Eyes*—Few recent observations on the human eye during starvation are available. Engelking (1923) and Harman (1925) discussed the condition known as phlyctenular conjunctivitis, which occurs in malnourished children. The disorder is apparently constitutional rather than local in character and may be (although this is not suggested by the authors) related to the ophthalmic disorders caused by a deficiency of vitamin A.

*Heart*—From the records of 4871 necropsies performed in American hospitals, Bean (1925, 1926) found the average weight of the heart about 10 per cent lower in emaciated than in well nourished patients. In the Russian cases of inanition reported by Stefko (1924, 1927a) there was a loss in weight and volume of the heart, greater in the young than in adults, and greater in females (especially at puberty) than in males. Microscopic examination revealed atrophy of the cardiac muscle. Stefko thought that the atrophy of the heart may be related to that of the gonads and suprarenal glands during inanition. Some heart weights were recorded also by Sedlezky (1924). Levine (1927) concluded from a review of the literature that the heart is more or less involved in every type of malnutrition, and that malnutrition is therefore a pathogenic factor of prime importance in various cardiovascular disorders.

*Blood and Blood Formation*—The results of inanition on the blood are exceedingly variable. Bakwin and Rivkin (1924) found an increase in the relative volume of blood in malnourished infants, which is contrary to the earlier observations of Marriott and Perkins. Lichtwitz (1923) concluded that, in general, the blood is relatively resistant to inanition. Lymphocytosis is regular and hydremia frequent, but anemia is not an early symptom. Curschmann (1923) observed somewhat variable effects of inanition on the blood during the war. It was his

Stephani (1923) noted the same changes in the thymus in infants after either acute or chronic dystrophy. Fat was observed persisting to a variable degree in the thymus cells.

In fasting new-born kittens, according to Dustin (1923), pyknotoses appear in the small lymphocytes of the thymus during the first day, becoming abundant on the second day, and undergoing disintegration and disappearance in numerous small areas by the third day. Hammar (1924) listed inanition and nutritional disturbances among the general factors causing involution of the thymus. He stated that in the rabbit after reduction of the thymus to 1 per cent of its original weight by incomplete inanition, complete recovery to normal weight was obtained within fourteen days by refeeding. Gunther (1924) found marked reduction in the thymus of fasting tadpoles (*Rana fusca*).

*Alimentary Canal*—According to Beuwkes (1926), the gastrointestinal symptoms of the victims of the Russian famine were sometimes slight, but dysentery was characteristic. Variot and his associates (1911, 1925) stated that gastric dilatation is not always caused by overfeeding, but may occur also through aerophagy in underfed, atrophic infants, as was previously noted by Lacau-Saint-Guilly (1913). Faehmann (1925) observed two cases of ileus in extremely emaciated women. Its pathogenesis is explained by the loss of fat in the omentum, which becomes reduced to a network of blood vessels. Intestinal loops slide into the omental openings. The pressure results in vascular obliteration with slow and progressive strangulation of the intestine.

Most of the recent studies concerned the alimentary canal in the lower animals. Busacchi (1916) claimed that in a dog starved thirty-five days the mitochondria of the intestinal epithelial cells were remarkably resistant, although they sometimes temporarily disappeared during refeeding. Watrin (1924), on the contrary, noted a disappearance of the mitochondria in the surface epithelium of the small intestine in starved rats. The parietal cells of the gastric glands became vacuolated.

Extensive studies on the regressive changes in the stomach and the intestine of underfed young albino rats were made by Miller (1927). The changes were most evident in the mucosa, which showed a variable degree of atrophy and degeneration, especially in the surface epithelium. In extreme cases, the villi appeared almost completely disintegrated. Sun (1927, 1927a) found a similar degeneration of the intestinal villi in albino mice starved only twenty-four hours. Apparent regeneration of the villi occurred within ten hours of refeeding, although four or five days were required for the recovery of the normal weight.

Jolly and Saragea (1924) found a loss of from 40 to 60 per cent in the appendix (cecum) of starved rabbits (which also showed a loss in weight of body of 30 per cent). The lymphoid follicles atrophied, the lymphocytes became scarce, with pyknotic nuclei. Many

ciates (1926) found a decrease of 47 per cent in the total leukocyte count, and of from 63 to 74 per cent in small and large lymphocytes, in albino rats starved 108 hours, with a slight relative increase at 132 hours. The neutrophils decreased in number more rapidly to a maximal loss of 48 per cent at thirty-six hours with a slight rise thereafter. Schaeffer (1925) observed a loss of about 85 per cent in the combined leukocyte and erythrocyte count in the "pumpkinseed" fish (*Eupomotis gibbosus*) during hibernation, but the blood count later returned to normal without feeding in spite of the progressive loss (up to 38 per cent) in weight.

*Spleen and Lymph Glands*—Deposits of hemosiderin in the spleen are much greater in chronic than in acute disturbances of nutrition, according to Stephan (1923). On account of marked individual variations, Hellman (1926) was unable to demonstrate a definite decrease in the amount of lymphoid tissue in the spleen during slight or moderate inanition. However, he found that a marked decrease occurred during prolonged starvation. Aron and Pogorschelsky (1926) found the weight of the spleen nearly parallel with that of the body in infants dying from either acute or chronic dystrophy. They reported that the spleen does not show a definite change in water content. According to Stefko (1927a), the spleen appears subnormal in weight in both young and adult persons who are starving, indicating a relatively greater loss of weight in the spleen than in the body as a whole during the starvation. The weights recorded by Sedlezky may also be consulted here. Stefko observed a marked atrophy of the splenic follicles, which often disappear. The blood vessels are distended. The various kinds of splenic cells (including nucleated erythrocytes in infants) are closely packed, and many, especially those of the myeloid type, show degenerative changes (nuclear pyknosis). The trabeculae and reticular tissue become prominent, especially in adults, in whom is seen almost complete atrophy of the splenic pulp.

Schwartz (1927) found the cellular reaction to infections in the lymphoid and myeloid tissues of the spleen markedly decreased by starvation in young mice. According to Dustin (1923), the atrophy of the lymphatic glands during inanition in new-born kittens is apparently due to emigration of the lymphocytes. Atrophy of the lymphoid structures in general during complete or incomplete inanition has been observed by various authors.

*Thymus*—All the recent work confirms the previous demonstrations of the susceptibility of the thymus to involution during all types of malnutrition, such involution was shown to have occurred by Ichok (1925), Variot (1925), Aron and his associates (1925, 1926), Stefko (1927a) and Boyd (1927). Stefko (1925a) found the typical atrophy and cell changes in the thymus of fetuses from starved mothers.



three days Geelmuyden (1923) reviewed the changes in content of glycogen and content of fat in the liver during fasting

Mayer and his associates (1914) did not find any decrease in the mitochondrial granules of the hepatic cells in the rabbit or dog starved with or without water Miller (1926), on the contrary, observed in underfed young rats a decrease in the size of the liver cells, and in the number of mitochondria, glycogen granules and cytoplasmic vacuoles Munzer (1925) confirmed Atapow's discovery that the number of binucleated liver cells decreases in starvation, with variations according to the type of diet (sugar, fat, protein)

Tiambusti (1896) noted in the amphibian, *Spelerpes fuscus*, a marked atrophy of the liver cells, with a slight decrease in the nuclei after it had been two and one-half months without food Hartmann (1918), on the contrary, found in fasting tadpoles of the toad (*Bufo vulgaris*) an apparent increase in the size of the liver cells Hertwig (1924) saw a marked decrease in the liver (he did not mention the cell size) in fasting tadpoles of *Rana fusca* Beig (1924) found a large accumulation of fat droplets in the liver cells of the salamander during the winter period of fasting This fat was evidently derived through the blood stream from the fat bodies, adipose tissue, muscle, skin, testis and other sources

In the trout (*Salmo fontinalis*) fasting up to three months, Plehn (1914) noted a progressive disappearance of the fat in the liver cells, which was soon restored on refeeding The glycogen appeared more resistant than the fat, and was never entirely exhausted Cotronei (1922) ascribed the marked change in the structure of the liver in *Petromyzon* (in comparison with the larval *Ammocoetes*) to a condition of inanition during the period of metamorphosis Esaki (1925) described atrophy of the hepatic cells and nuclear changes as taking place during starvation in the fish, *Oryzias latipes* D'Ancona (1922, 1926, 1927b) made extensive observations on the liver of the eel (*Anguilla*) during a progressive inanition up to 657 days The volume of the liver cell was reduced about 90 per cent, and that of the nucleus somewhat less Hyperemia and relative fibrosis were noted

*Pancreas and Submaxillary Gland*—Aron and his associates (1925, 1926) found the decrease in the weight of the pancreas nearly proportional to that of the body in both acute and chronic nutritive disturbances in infants There was a slight increase in the content of water of the pancreas Stefko (1924), on the contrary, asserted that, in starvation, the pancreas does not lose weight as do most other organs, but often increases In this connection, the weights recorded by Sedlezky may be consulted The microscopic structure is unchanged in the earlier stages of inanition, but in later stages it shows marked hyperemia, hemorrhages, degeneration and necrosis (hemorrhagic pan-

large phagocytic cells appeared in the connective tissue. On refeeding, almost normal structure was recovered in fifteen days. Simple atrophy with some hyperemia of the gastric mucosa was observed by Guarino (1927) in guinea-pigs and pigeons starved with or without water.

Baichiesi (1924) found extreme atrophy of the mucosa in the esophagus, stomach and intestine of the tortoise (*Emys orbicularis*) fed water alone for from five to twenty-six months. The epithelial cells were reduced from 83 to 97 per cent in volume, the nuclei from 75 to 78 per cent. Refeeding tests showed that recovery was possible after seven months of starvation. Gunther (1924) noted great reduction in the size of the intestine in starved tadpoles (*Rana fusca*). Corti (1920, 1920a, 1921, 1922) made a special study of the migratory cells in the intestinal epithelium during inanition in various amphibia and fishes. Yung (1914) found a reduction to one-sixth in the size of the intestinal epithelium in inanition in various amphibia and fishes. The loss was chiefly in the cytoplasm, the nuclei being more resistant. D'Ancona (1921, 1922, 1926, 1926a, 1926b, 1927, 1927b) made several intensive studies on the alimentary canal of the eel (*Anguilla*) starved up to 657 days, with a loss of 61.5 per cent in weight. The gastric gland cells lost about 80 per cent in volume, and the nuclei 42 per cent, the intestinal epithelial cells 65 per cent, and the nuclei 53 per cent. Evidence of a decrease in the number of cells was not found. The histologic changes were less marked in young than in adult eels.

*Liver* —Stepham (1923) found that, at necropsy, the liver in cases of acute nutritive disturbance (especially with signs of intoxication) almost always shows marked fatty changes, which are slight or absent in cases of chronic malnutrition. Stefko (1927a) observed a reappearance of blood-forming cells in the liver in famine-stricken adults as well as children. Some weights were recorded by Sedlezky (1924). Bean (1925, 1926) found an apparent depression of the weight of the liver associated with emaciation in 4,871 records of necropsies in hospitals of New Orleans and Baltimore. These records showed the liver averaging about 15 per cent heavier in the well nourished patients.

Junkesdorff (1921) found that the liver lost weight more rapidly than the body in dogs fasting eleven days. The fat of the liver either persisted longer than the ordinary fat or was replenished by immigration from the latter through the blood stream. Salvioi and Sacchetto (1921) noted a decrease in neutral fats and fatty acids, with the appearance of lipoids, in the liver cells of dogs and guinea-pigs starved for various periods, up to a loss of about 41 per cent in body weight. The distribution of fat in the liver cells varied in the two species. Wolff (1924) found that in lean white mice the slight amount of fat in the liver was removed within twenty-four hours of fasting, while in fat mice the larger amount of fat in the liver was not all removed in

(1924) noted in the cells of the renal tubules in fasting white mice a transient fatty infiltration which disappeared if the inanition was prolonged or if normal feeding was resumed

*Female Reproductive System*—The inhibition of menstruation by malnutrition that was noted by numerous observers in various countries during the famine consequent on the war, was found likewise by Anitschkoff and Sawodski (1922) in Russia. The effect may long persist in the form of a hypoplasia of the genital tract, which, according to Kustnei (1926), increased in the Halle clinic from 0.8 per cent of the cases in 1919 to 1.5 per cent in 1925. Siemens (1926), however, doubted whether the decrease in the number of births in Germany during the war could be ascribed to inanition. The statistics do not show any significant change in the relative number of twins and triplets, in contrast with the observations of Richter (1926) on domestic animals.

In contrast with the relatively slight effect on the weight of the testis, Aron and his associates (1925, 1926) found a great loss in the weight of the ovary in dystrophic infants. Among 120 cases of starvation, in which the patients were aged from 7 to 40, Stefko (1924a, 1927, 1927a) could not find a single mature ovum. The follicles had undergone marked involution and atresia, and a few persistent primordial follicles were seen. The interstitial gland cells also had become rudimentary, and the ovary consisted chiefly of fibrous tissue. The age of puberty was greatly retarded. The persistent effects of earlier malnutrition were further shown by the examination in 1926 of 148 girls from 14 to 18 years of age. Of these, 28 per cent showed general hypoplasia of the sexual organs, 8 per cent infantilism and 21.3 per cent marked retardation of puberty (of menses, mammary development and the like). Some ovarian weights were noted by Sedlezky.

According to Richter (1926), a distinct reduction in fertility of domestic animals (sheep, goat, swine) was caused by underfeeding in Germany during the war. Especially in sheep there was not only a decrease in the number of births but a remarkable rarity of twin births. Blum (1924) found that a change of the sex ratio during underfeeding did not occur in white mice. Martino (1927) noted in starved or underfed hens ovarian disturbances and a suspension of ovulation, with recovery on proper refeeding. Aragei (1925a) described an inhibition of gonadal development and a degeneration of the gonocytes in fasting tadpoles of the toad (*Bufo vulgaris*).

*Male Reproductive System*—Aron, Lasch and Pogoschelsky (1925) and Aron and Pogoschelsky (1926) did not find any indication of a loss in weight or change in content of water of the testis in dystrophic infants. Anitschkoff and Sawodski (1922) ascribed the depression of sexual function in adult males during the Russian famine to atrophy of

creatitis) In chronic cases, there may be a hypertrophic cirrhosis The islets of Langerhans soon disappear completely Seyfarth (1920, 1924) and Jorns (1927) reached the opposite conclusion, finding an enlargement and an increased number of pancreatic islets in a case of death from starvation Frequent transitions from acini to islets were found Jorns described a slight atrophy of the pancreatic acini and an increase of the interlobular connective tissue

Grinew (1912) reviewed the earlier literature on the controversy as to the possibility of the transformation of pancreatic islets into acini (and vice versa) through disturbances of nutrition Cecil (1911) measured and counted the islets in six dogs He concluded (confirming Bensley) that inanition does not have an appreciable effect on the number, size or structure of the pancreatic islets Martius (1915) found numerous islets in the pancreas of a starved man, but did not succeed in producing an increased number of islets by the starvation of frogs, mice, guinea-pigs and chickens Watim (1924), however asserted that, in rats starved six or seven days, in spite of pancreatic atrophy, the old islets proliferated and many new islets arose by transformation of the acini Further data were cited by Jackson (1925) The question as to the effect of inanition on the pancreatic islets is apparently still unanswered

The ratio of nucleus to plasma in the pancreatic cells of the white rat, normal and starved, was investigated by Dolley (1925) Ma (1924) found the mitochondria of the pancreatic acinus cells changed from filamentous to irregular granular form in guinea-pigs fasting up to twenty days The normal structure was recovered on refeeding

*Submaxillary Gland*—Takagi (1925) observed little change in the ordinary alveolar cells of the submaxillary gland in young and adult cats fasting from twenty-four to ninety hours The demilune cells, however, became larger, with more numerous secretory granules, but fewer mitochondria The nuclei appeared darker and richer in chromatin

*Kidney*—A study of 4,871 records of necropsies performed in American hospitals indicated to Bean (1925, 1926) that the average weight of the kidney is about 15 per cent greater in well nourished than in emaciated persons Emaciation in man apparently affects the kidneys less than the heart or the liver Some weights bearing on this question were given by Sedlezky (1924) In a study of the white rat, Hayashi (1924b) placed the kidneys in the group of organs which lose weight more slowly than the body during inanition Fionstein (1922) noted a characteristic diuresis and an increase of nonspecific infections of the urinary tract during famine in man Schwariz (1927) similarly found a decreased resistance (as indicated by the cellular reactions) to experimental infections in the kidney in starving white mice Wolff

by Champy (1922, 1924) in adult *Triton alpestris*. In the male triton, inanition inhibits spermatogenesis and causes an involution of the spermatogonia. It is held that the male sexual gland on refeeding may be transformed into the female.

*Suprarenal Glands*—In dystrophic infants, the loss in weight of the suprarenal glands is nearly proportional to that of the body, according to Aton and his associates (1925, 1926). Stephan (1923) found that the fat content of the suprarenal cortex nearly or entirely disappears during acute infantile malnutrition (especially with intoxication), but is variable in chronic malnutrition. Fockermann (1925) and Stefko (1926b) described the changes in the suprarenal glands resulting from the Russian famine as occurring in three stages: (1) an acute stage, with occasional hemorrhages in the cortex, and oftener atrophy of the zona fasciculata and of the medulla, followed by proliferation of the reticular stroma, and by fibrosis in the medulla; (2) the appearance of degenerative changes in the zona glomerulosa, zona reticularis and especially in the medulla (with a fall in blood pressure), and (3) the final stage, with vacuolar degeneration of all cortical layers and complete destruction of the medulla, a change in the pigmentation of the skin does not occur. Stefko (1926) concluded that the third type of suprarenal involution with hypoplasia of the medulla may persist as a permanent condition, even after the period of inanition is past. The suprarenal weights in such cases (adult) appeared subnormal, averaging from 7 to 8 Gm. in males and 10 Gm. in females.

In fetuses from starved mothers, Stefko (1925a) found the suprarenal glands normal in appearance and structure. In the postnatal cases of starvation (1927a), in children, the suprarenal glands usually appeared above normal in weight. This increase was ascribed to general hyperemia (often hemorrhages) and also to an increase in connective tissue, especially in the medulla. The parenchymal cells of both cortex and medulla underwent progressive degenerative and atrophic changes, which were described in detail and which corresponded with the three stages described by Fockermann and Stefko. The observations by Stefko and other Russian investigators were also reviewed by Ichok (1925) and Newsoroff (1927). Some weights of the suprarenal glands were given by Sedlezky (1924).

In the white rat, Hayashi (1924b), as did most earlier investigators, found an increase rather than a decrease in the weight of the suprarenal gland during inanition. The cells showed a variable degree of shrinkage, somewhat proportional to the length of the test. Hett (1926, 1926a) studied the effect of acute or chronic inanition on the suprarenal glands of both younger and adult white and gray mice. Degeneration of the cortical cells to form syncytial masses, containing pigment occurred in the zona reticularis and adjacent zona fasciculata. The

the seminal vesicles and a decrease in the internal secretion Stefko (1924a, 1924b, 1927, 1927a) made an extensive study of the question Among 800 undernourished Russian boys between 7 and 16 years of age, cryptorchism occurred in 216 (27 per cent) The cryptorchism was ascribed to a secondary ascent of the testis, associated with a shortening of the cremaster muscle The percentage of cryptorchism was somewhat less in Jewish (13 per cent) and Tartar boys (from 8 to 10 per cent), and occurred chiefly in boys between the ages of 10 and 13 years Puberty was greatly retarded, and the external genitalia in general remained undeveloped The testis in the starved boys presented a general atrophic destruction of the seminiferous tubules with repression of spermatogenesis and with proliferation of the connective tissue Similarly, of thirty-five starved adult men (from 16 to 42 years of age), seventeen did not have spermatozoa in the seminiferous tubules The Sertoli cells and the interstitial cells of Leydig appeared to be the most resistant to inanition The persistent effects of earlier inanition were observed in the examination of 851 outpatient boys in 1926 Of these, 309 (36.7 per cent) showed symptoms of genital hypoplasia Some weights for the testis were recorded by Sedlezky

In adult mice starved from four to ten days, among which the maximal loss was about one third of the body weight, Stieve (1923) found little if any effect on the size of the testis or on spermatogenesis, but a marked atrophy of the interstitial cells The penis, prostate and seminal vesicles appeared normal, and copulative ability was unimpaired Saller (1926) similarly studied the effects of acute and chronic inanition with loss of about one fourth in the body weight in white mice There was evidently a loss in the weight of the testis, and atrophy of both seminiferous and interstitial tissues, though individual variations made the conclusions somewhat uncertain Stone (1924) found retardation in copulative age, spermatogenesis and development of the accessory sexual apparatus in rats underfed (at maintenance) for twenty days, the tests beginning at the age of 20 or 30 days, but he did not find any appreciable effect in tests beginning at 45 days of age

In pigeons without food, according to Amantea and Martino (1925), sex desire is lost in a few days Restoration of the sexual functions is much slower than recovery in weight on refeeding This was observed also in chickens by Martino (1926, 1927) In cockerels, the effect of inanition on the germinative function of the testis (measured by breeding tests) appeared earlier and persisted longer after refeeding than that on the endocrine function The endocrine function of the testis was measured by the size of the comb, which is markedly reduced by inanition

For amphibians, the effects of inanition on the gonads was investigated by Arager (1925a) in tadpoles of the toad (*Bufo vulgaris*) and

variable degree of hypoplasia in the glandular tissue, a decrease in the number of eosinophil cells and a relative increase in the basophil cells and granules. There was also an increased formation of colloid. The changes, however, were of comparatively slight importance.

#### PARTIAL INANITION

The effects of partial inanition will be considered under the heads of deficiency of protein, deficiency of minerals, deficiency of water and deficiency of vitamins. The effects of a dietary deficiency of fat are ascribed chiefly to the associated deficiency in the fat-soluble vitamins, A, D and E. Burr (1928), however, found a caudal dystrophy in rats on diets fat-free (except for the known vitamins), and Baldwin (1928) described marked lesions in the testis and suprarenal glands in rats on a cholesterol-free diet.

#### EFFECTS OF A DEFICIENCY OF PROTEIN

*Malnutritional Edema*—The generalized or localized edema frequently found accompanying chronic inanition in man ("famine edema") is probably associated with diets variously deficient in part, as well as with general caloric insufficiency. The available evidence, however, seems to indicate that a dietary deficiency of protein is the most important pathogenic factor. According to Lubarsch (1921), the characteristic lesions of the "Oedemkrankheit" include (1) a marked depletion of fat and lipoids, with a persistence of lipid remnants in muscle, cartilage cells and the suprarenal cortex, and increased lipoidal pigmentation in various regions, (2) atrophic changes with pigmentation, especially in the heart and the liver, (3) a variable destruction of red blood cells, associated with deposits of hemosiderin in various organs, and (4) a tendency to serous exudates and hemorrhages, especially in the alimentary canal, which are due to direct injury of the endothelial cells of the capillaries, and not to cardiac or renal diopsy.

Anitschkoff and Sawodski (1922) observed that in the Russian famine the sometimes enormous edemas were associated with a slow pulse rate and a weakened heart, without lesions of the kidneys. The location of the edema was variable, but oftenest in the face or the extremities. Beeuwkes (1926) described the Russian "hunger edema" in detail, and gave many photographs. The most characteristic symptoms were edema, polyuria without albumin, bradycardia and bulimia. The edema began first in the lower limbs, and extended variably upward. There was sometimes a general anasarca, amounting to 25 per cent of the body weight. The heart suffered severe damage, and sudden death from heart failure was common. The blood pressure was low, except in patients with arteriosclerosis. The gastro-intestinal symptoms were variable, but dysentery was characteristic. The nervous symptoms

effects were less marked in the medulla, where pigment granules were found in the capillary endothelium

*Thyroid Gland*—The importance of hypothyroidism resulting from the atrophy of the thyroid gland during famine has been emphasized by Cuischmann (1921, 1923) and Lichtwitz. Fukushima (1924) found the thyroid gland in dystrophic infants subnormal in weight in thirty-four of forty-five cases. He summarized the changes as follows: surface, brownish red, frequently nodular; consistence, rather firm; size and weight, decreased; follicles, decreased; epithelium, cubical or often flattened; colloid, thin; interstitial connective tissue, somewhat frequently increased. Aron and Pogorschelsky (1926) found the weight of the thyroid gland (percentage of final body weight) above normal in dystrophic infants, and therefore concluded that it had lost little. Stefko (1925a) noted a normal appearance and structure of the thyroid gland in the fetuses from starved mothers, but (1927a) in malnourished children and adults, he observed that it was subnormal in weight, both absolutely and relatively. A microscopic examination revealed atrophy of the thyroid follicles, with a variable degree of epithelial flattening and desquamation, and also changes in the colloid content. Thyroid atrophy and involution during malnutrition were reviewed also by Ichok (1925) and Newsonoff (1927). Some weights of thyroid and parathyroid glands were given by Sedlezky (1924).

Mitochondrial changes in the thyroid epithelium were studied by Nicholson (1924) in rabbits and guinea-pigs subjected to various conditions, including a fast of from three to six days and a diet deficient in vitamin B. The filamentous mitochondria became fragmented and granular in structure. Chang (1925) confirmed Jackson's results showing atrophy or degeneration of the thyroid from chronic starvation in the albino rat.

*Parathyroid Glands*—According to Cuischmann (1923), the parathyroid glands may also be affected during inanition (Hungetetanie of Lichtwitz and others). The changes were described by Stefko (1927a), whose work was also reviewed by Newsonoff (1927). In malnourished children and adults, the parathyroid glands became considerably enlarged and hyperemic. Follicles appear containing a variable amount of colloid. The parenchyma is poor in cells (basophil and chief cells), sometimes mast cells are numerous. In some cases, the cells show hydropic degeneration.

*Hypophysis*—Observations of the hypophysis, such as were made by Sedlezky (1924) in starved Russian children, were reported also by Stefko (1927a). Sedlezky did not find any change in the macroscopic appearance and but slight loss in the weight of the hypophysis. The anterior lobe (especially in children) appeared hyperemic, with a



phan on the thyroid gland are therefore comparatively slight, although general emaciation and death result

According to Beard (1926), cystine cannot be successfully replaced by taurine, although both contain sulphur, in the diet of mice. Cystine is the limiting amino-acid factor in casein when the casein forms 12 per cent of the diet. The addition of 0.5 per cent of cystine causes growth at a rapid rate. The records of the experiments of Hayashi (1924, 1924d), including those on the effects of a deficiency of protein in the white rat, were inaccessible.

Although an increased amount of protein is required by the rat during reproduction and lactation (as was made clearly evident by Simmonds in 1924), Maynard and Bender (1928) found that in the rat during this period a 50 per cent ration of protein did not show any advantage over an 18 per cent ration.

#### EFFECTS OF A DEFICIENCY OF MINERALS

In this section of the paper will be included, first, some recorded observations on the effects of mixed or multiple deficiencies of minerals. The studies on rickets, although involving a disturbance in the relations of calcium and phosphorus, are considered under the head of vitamin D. McCollum, Simmonds and Becker (1925) found that the previously described "salt ophthalmia" in rats cannot be induced by feeding excessive amounts of any one element or ion. Possibly the effect of the salt factor is simply to damage the vitamin A present in the diet. Orr (1924) reviewed the significance of various mineral elements (calcium, potassium, iron, iodine and other elements) in animal nutrition and the effects of a deficiency of minerals in children and adults. The mineral balance is held to be even more important than the vitamins.

Haag and Palmer (1928) also emphasized the importance of the dietary balance of calcium, phosphorus and magnesium salts as essential for normal health and growth in rats. Various combinations resulted in an enlargement and a hemorrhagic condition of the suprarenals. One diet (with the content of calcium low and of magnesium and phosphorus high) in a few cases apparently produced cystitis and phosphatic calculi. The salts also appeared to be important in relation to some of the vitamin requirements. Chidester, Eaton and Thompson (1928) believed that vitamins are effective through their mineral content.

Khigler and Geiger (1928) found that a dietary deficiency of any of the important salts (potassium, sodium, calcium), except magnesium, caused dwarfing of young rats. A deficiency in any of these salts also lowered the resistance to infection with trypanosomes.

Morr (1924) fed rabbits a diet of hydrous wool fat, bacon fat and cholesterol (a diet deficient therefore in protein and vitamins, as well as in salts) and produced degenerative changes in the teeth. Although

were inconstant. In the blood, there was a tendency to hydiemia. The red cell count sometimes decreased to 2,500,000, the average being 4,000,000. Leukopenia with a decrease in the count of polymorphonuclears and a relative lymphocytosis was frequent. Some authors maintained that the type of edema could be differentiated according to the leukocytic formula.

The factors in the pathogenesis of famine edema were discussed by Kusnezoff (1922), Kabanoff (1923) and N. Anitschkoff (1925). From his experience with "hunger edema" in Germany, Curschmann (1922, 1923) emphasized the atrophy of the thyroid gland as the most important lesion, the resultant edema being related to the myxedema of hypothyroidism. Jaureguy (1925) described an extreme edema of the legs, resembling elephantiasis, in an infant which had been fed for months on a thin vegetable soup. On suitable diet, the edema disappeared within a week. Hoelzel (1928), from experiments made on persons while fasting, concluded that protein starvation is the primary factor in the pathogenesis of nutritional edema. He found also that although colds were not ordinarily contracted during the prolonged fasting, they developed almost invariably after such periods, when edema was also prominent.

*Experiments on Animals*—Stammers (1926) reported some hypertrophy of the suprarenal glands, disappearance of cortical lipoids and an increased epinephrine content in cattle with malnutritional edema (avitaminosis?). Moise and Smith (1924) and Smith and Moise (1924) found that in rats poisoned with chloroform regeneration of the hepatic cells occurred during fasting or on a diet of gelatin, though less rapidly than on diets containing gliadin or casein as the protein component. Thus, regeneration of the liver can occur on diets which do not permit general growth of the body.

Light (1927) observed that a deficiency of protein, phosphorus or vitamin A caused a lengthening of the estrus cycle in the albino rat. Hartwell (1925) noted a loss of fur in pied rats when potato or white bread was their sole source of dietary protein. The substitution of brown bread or oatmeal, or the addition of gluten, gelatin or caseinogen to the bread diet prevented the loss of fur.

Chang (1925, 1926a) tested Cramer's theory that tryptophan is a dietary essential as the mother substance of the thyroid hormone. He concluded that in white rats tryptophan is necessary for maintenance of the body, but probably not directly essential to thyroid activity. Abel and his associates (1925), from somewhat similar feeding experiments, reached the opposite conclusion that tryptophan is essential to the normal functioning of the thyroid gland, but held that most of the needed tryptophan can be supplied through the blood stream from other tissues of the body. The effects of a dietary deficiency of trypto-

amount of dietary calcium was shown by Stepp (1925) Rats on a mixture of oatmeal, casein, dextrin and sodium chloride with 1.5 per cent calcium carbonate developed severe keratomalacia only, but with the calcium carbonate increased to 3 per cent, rickets appeared in addition to the keratomalacia

Mellanby and his associates (1924) concluded that a shortage of calcium and calcifying vitamin is responsible for caries in the teeth of children Toverud (1927) held that similar dietary deficiencies are the chief factor in producing dental caries of women during pregnancy These conditions are probably closely related to rickets Lebedev (1927) still adheres to the older view that rickets is not a specific disorder but a variable symptom-complex that may be produced by various means, including that of simple deficiency of calcium Corlette (1928) held that a deficiency of calcium and phosphorus can cause a nervous disorder closely resembling that produced by a deficiency of vitamin B in man and lower animals Among the morbid conditions involving these mineral deficiencies, in which nervous symptoms often occur, are polyphagia, earth-eating, bone-chewing, coprophagia, rickets, osteomalacia, spasticity, paraplegia, tetany, and the *stijfziekte* and *lamziekte* of South African cattle

According to Simmonds (1924) the growth of rats on a diet in which the calcium content was low was only half the normal rate Mother rats on such diets might produce and nurse young, but often they broke down on account of a loss of calcium from the skeleton Kennedy (1926, 1926a) found that a deficiency of calcium in a diet otherwise adequate induced sterility in both male and female rats, probably through effects on the germ cells The nature of the sterility was uncertain Ovulation and the formation of normal corpora lutea took place, but signs of implantation or resorption did not appear in the uterus Macomber (1927) concluded that the deficiency of calcium did not produce sterility in the adult rat, but did affect fertility by increasing the intra-uterine mortality Since the prenatal skeleton is largely cartilaginous, the mother rat may be able to supply from her own reserves sufficient calcium for normal fetal growth During lactation on the diet low in calcium, however, the maternal reserves are exhausted and the young soon become stunted in growth as a result of the deficiency of calcium

Buckner, Martin and Peter (1925) found that larger eggs (yolks and white) were produced when calcium carbonate (crushed oyster-shell) was added to the corn-wheat-buttermilk diet of hens

Hirsch (1925) and Day (1928) emphasized the indispensability of calcium for plant growth, as shown in beans, peas, buckwheat and other plants The growth of the root is greatly injured by a deficiency of calcium, and a degeneration of the nuclei and the chlorophyll granules may result

the enamel appeared normal, the dentinal ground substance was necrotic and the dentinal tubules filled with fat. The odontoblasts were atrophic and fatty infiltration appeared in the pulp cells and connective tissue cells of the periodontal membrane. Changes were also found in the cementum and alveolar bone.

Osborne and Mendel (1923) reported a failure of growth in rats when the salt content of the diet was reduced to 1 per cent or less. Complete recovery and growth were not obtained on the addition of salts to the diet later. The records of the work of Hayashi (1924, 1924d), including that on the effects of a deficiency of salts in rats, were inaccessible.

Yamasaki (1923) studied the effects of various dietary deficiencies on the gonads of white mice. The results of the deficiency of salts were similar to those of a deficiency of vitamins or of total inanition, including a disturbance of spermatogenesis in the testis and follicular atrophy in the ovary. This work was continued by Hinabayashi (1924), who investigated the effects of a deficiency of certain elements (sodium, chlorine, calcium, magnesium, potassium, phosphorus, iron), singly or in certain groups. Deficits of calcium, phosphorus and magnesium (individually) caused the most severe effects. Normal spermatogenesis apparently required the presence of various salts. The removal of one ion might result in the disturbance of other ions.

Thompson (1926) obtained normal growth in albino mice on a diet (skim milk powder 20, casein 24, starch 20, butter fat 32, yeast 2) with an ash content of only 0.7 per cent. A lowered hemoglobin content was noted, especially in the second generation. The bones were delicate. Obesity was common in old age, more frequently in the females. "Fatty infiltration was found in all the internal organs besides large quantities of fat in the usual storage spaces. There were a few cases of moist looking fur, but, more commonly, the fur was rather thin and without lustre."

In order to throw more light on the significance of mineral nutrition in animals, Hirsch (1925) reviewed the subject of minerals in plant nutrition. The cations  $K^+$ ,  $Na^+$ ,  $Ca^{++}$ ,  $Mg^{++}$ ,  $H^+$  and  $Fe^{+++}$  and the anions  $Cl^-$ ,  $NO_3^-$ ,  $SO_4^{=}$  and  $HPO_4^{=}$  appear essential although the exact function of each is not clear. The question of mineral nutrition in plants was reviewed also by Palladin (1926), who compiled an extensive bibliography.

*Deficiency of Calcium*—McCollum (1926) stated that "probably a lack of calcium, and the taking of a diet disproportionately rich in phosphorus and lacking in vitamin D, are the faults of greatest significance in the diet of many Americans." This combination would (he thought) lead to rickets. This form of malnutrition will be discussed later under the head of vitamin D. The marked effect of slight variations in the

ventive and curative agent for goiter, denied that this proved deficiency of iodine to be the cause. Many persons in regions where there is supposedly a deficiency of iodine, do not have goiter, and many goiters occur in coastal regions, where there is an abundance of iodine. Liek (1927), who studied 1,286 cases in the Danzig district, for similar reasons opposed the theory that goiter is caused by a deficiency of iodine.

*Deficiency of Iron*—McGowan (1924, 1924a) and McGowan and Crichton (1924) described a disorder in pigs the mothers of which had been fed an iron-poor diet of distillers' draff, maize and whitefish meal during pregnancy and lactation. The young pigs became fat and stocky in build and anemic (the hemoglobin content falling as low as 20 per cent), and showed enlarged hearts, effusions into the serous cavities, and sometimes, in the later stages, fatty changes and necrosis in the hepatic lobules. The disease appeared to be identical with the so-called cotton seed meal poisoning (really a disorder due to a deficiency in the diet, according to McGowan). It was found that the disease could be prevented and cured by the administration of ferric oxide in the food.

Hart and his associates (1925) observed that rabbits on a diet of cow's milk developed marked anemia. The addition of inorganic iron did not cure this anemia, unless there was also added fresh cabbage, alcoholic extract of cabbage, corn meal or chlorophyll. Recently, the same investigators (Waddell and others, 1928) showed that a similar anemia induced in young rats by a diet of milk was cured by the feeding of either dried liver (1.72 Gm daily) or the ash of the same amount of liver (containing 0.5 mg of iron), but not by the addition of the iron salts alone.

*Deficiency of Other Minerals*—The effects of a deficiency of potassium on the development of the sea urchin (various species) was investigated in detail by Runnstrom (1925). There was a disturbance of the colloidal condition of the protoplasm, affecting lipoids and protein and distribution of the water. The mitotic figures were deformed in various ways. Amitosis sometimes occurred. The form of the segmented ovum was abnormal. The vegetative pole of the ovum was affected more than the animal pole. The gradient of sensitivity (from greater to lesser) was in the following order: mesoderm, entoderm, ventral ectoderm, dorsal ectoderm. Recovery was possible in normal sea water, if the injuries had not been too great.

That magnesium is necessary for the growth and maintenance of white mice was indicated by the experiments of Leroy (1926). Klugele and Geiger (1928), however, did not find any retardation in the growth of rats on diets deficient in magnesium.

McLean and Gilbert (1925) found that a deficiency of manganese caused chlorosis in spinach. The work of McHague (1928) likewise

*Deficiency of Phosphorus*—Stammeis (1926) placed two adult albino rats on a diet without phosphates. They died in forty-one days with a loss of 40 per cent in weight. The yellow bone marrow was gelatinous, but the organs appeared normal. The suprarenal glands were not enlarged, and showed an abundant lipid content in all three cortical zones. Light (1927) found that a deficiency of phosphorus in the diet prolonged the estrus cycle in the rat.

Eckles, Becker and Palmer (1926) made an extensive investigation of a disorder in cattle similar to that previously appearing in various parts of the world. The symptoms include depraved appetite ("pica") and markedly retarded growth and dwarfing of the adults with a disproportionate enlargement of their heads. The ovaries are atrophied, the estrus is inhibited, and fertility is markedly subnormal. The bones show osteomalacia and osteoporosis, especially in the ribs. The joints become exceedingly stiff and creak loudly. The disease is apparently caused by a deficiency of phosphorus (not calcium) and can be prevented or cured by feeding bone meal or simply inorganic phosphates.

*Deficiency of Iodine*—The relationship between a deficiency of iodine and goiter is an unsettled question. McClendon and Hathaway (1924) published further data showing the relative content of iodine in the food and water from goitrous as compared with nongoitrous areas. Skinner (1924) presented twelve cases of congenital goiter ascribed to a deficiency of iodine in the maternal diet. The pathologic changes varied from a simple parenchymatous goiter without symptoms to marked enlargement with complete tracheal compression and dangerous cystic conditions. Marine (1924) gave an extensive review of the theory that simple goiter is caused by a deficiency of iodine. His conclusion was that "the gland cells begin to hypertrophy when the iodine store falls below a given level (less than 0.1 per cent in the animals studied), and continue this hypertrophy and hyperplasia until exhaustion atrophy or recovery supervenes. By anatomical recovery one means the involution of the active hyperplasia to the colloid or resting stage and not, as some have supposed, the disappearance of the thyroid enlargement." Tanabe (1925) similarly concluded from feeding experiments that the lack of iodine is the basic etiologic factor in the production of goiter (*Struma diffusa parenchymatosa*) in rats. Extremely small amounts of potassium iodide inhibited the glandular hyperplasia. The administration of iodine likewise prevents the condition of exophthalmia and thyroid hyperplasia in young trout (Hamre and Nichols, 1928), and inhibits the compensatory hypertrophy of the thyroid after partial resection in dogs (Schmitz-Moorman and Meis, 1928).

On the other hand, some are still skeptical regarding the theory that goiter is caused by a lack of iodine. Oswald (1927) of Zurich, for example, though admitting that in general iodine is valuable as a pre-

The recent work on the effects of a deficiency of water may be classified as related to (a) effects on infants, (b) effects on the blood, (c) experimentally produced effects on animals and (d) effects on plants

*Effects on Infants*—Mannott (1923) stated that the two chief nutritional disorders of infancy are athrepsia (caused by quantitative or qualitative inanition) and toxicosis. The toxicosis or "alimentary intoxication" may arise in either athreptic or previously healthy infants. It is an acute disturbance marked by sudden loss of weight, exhaustion, fever, dry and grayish skin, usually diarrhea, vomiting and neural disturbances. The varied causes all result in depletion of the general water reserves. This depletion produces the marked fall in weight, and the changes in the blood (to be mentioned later)

Finkelstein (1921) held that among other effects a loss of water may cause infantile alimentary toxicosis. He believed, however, that the immediate pathogenic factor in this disease is a disturbance of the liver, which interferes with its detoxifying function. Stephani (1923) found fatty changes in the liver nearly constant in such cases. Stolte (1923) also recognized the loss of water as an important factor in the pathogenesis of infantile intoxication, but held that the dehydration affects the cell protoplasm throughout the body. Kleinschmidt (1923) thought the primary effect is on the intestinal wall, lesions of which permit the absorption of toxic materials (autotoxemia). Schiff (1924) and Schiff, Elsasberg and Bayer (1924) concluded that in human infants a shortage of water produces toxic symptoms only when the diet contains sufficient protein. Increased permeability of the intestine may permit the absorption of toxic factors (incompletely broken down proteins). These toxins, however, are usually detoxified in the liver, so that the hepatic lesions (often seen at autopsy) may be of primary importance. Further work on the relation of a deficiency of water to alimentary toxicosis will be cited later in the section on experimental results.

Rosenbaum (1924) gave a complete review of the literature together with observations on eighty-eight cases of infantile intoxication. He held that the clinical symptoms depend on the rapidity of the dehydration, which may be caused by diarrhea, vomiting or excessive pulmonary evaporation. In addition to the changes in the blood (to be mentioned later) an increased amount of liver fat was found, usually but not always. Fatty infiltration of the liver may occur also in non-toxic cases. The loss in skin turgor is characteristic. Definite changes in water content or the histologic structure of the brain were not observed (this is contrary to the observations by Bessau).

Schiff and Bayer (1925) observed that in children on a relatively dry diet (dry milk, potato flour, butter and sugar) the kidneys are

confirmed the theory that manganese is a nutrient necessary to plants. Warrington (1926) found also that a deficiency of boron affected both the external morphology and the internal anatomy of the bean plant.

Hart, Steenbock, Waddell and Elvehjem (1928) concluded that copper in the diet was essential for a normal condition of the blood and the body. In anemic rats on a diet of milk, the improvement that follows the addition of dried liver or the ash of liver, corn or lettuce to the diet is ascribed to the presence of copper rather than of iron.<sup>1</sup> McHargue (1928) believed that copper is likewise necessary in the nutrition of plants.

Sievers (1928) found that a deficiency of nitrogen in the soil produces in arid regions a nutritional disorder of orchard trees with a peculiar effect on the development of the leaf and the structure.

The effects of a deficiency of oxygen observed by Vacek (1926) in white mice are of interest for comparison with the effects of deficiencies of minerals. There is a progressive hypertrophy of the heart (up to 30 per cent) and of the lungs. The increase in size of the heart is secondary to that of the lungs; in an inverse fashion, the hypertrophy of the heart being greater in cases in which the lungs are insufficient in size.

#### EFFECTS OF A DEFICIENCY OF WATER

Since water forms a large and essential component of living protoplasm a deficiency of water (giving rise to aqueous inanition) in general has markedly injurious effects on all living organisms. Siebeck (1923) reviewed the general significance of water in the body, and the factors concerned in the production of edema. Staub (1924) traced the processes involved in the entrance of water through the intestinal wall, the exchange of water between the tissue cells and the blood or lymph and the excretion of water through the kidneys, lungs and skin. Staub held with Stolte (1923) that water is of fundamental importance, because protoplasm is in a colloidal state. Schiff (1924) and Thoenes (1924) likewise emphasized the importance of the water content of the body from the point of view of colloidal chemistry. Thoenes distinguished between free water, which is easily separated from the tissues, and bound water, which is colloidal. The bound water (in muscle) is normally about equal to the fat-free dry substance, but may become relatively reduced in certain abnormal conditions of exsiccation (toxic diarrhea).

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<sup>1</sup> The factor of liver that is effective in anemia in rats is apparently different from that which is curative in pernicious anemia in man. The latter factor, according to Cohn and others (1928) is either a nitrogenous base or a polypeptide of which but 0.6 Gm. daily produces a pronounced response of reticulated blood cells.



(1926) obtained similar results, including a loss of weight of from 47 to 99 per cent in four dogs within twenty-four hours through diuresis. The blood was greatly concentrated, as shown by the measurements of the hemoglobin content.

In experimental intestinal obstruction in dogs, Foster and Hansler (1925) found that lack of intake of water together with vomiting caused a marked dehydration with increased viscosity of the blood, high concentration of red cells and of hemoglobin, a decreased volume of blood flowing in the extremities and a marked loss in weight. The blood pressure and the respiratory rate were each low, the pulse rate was almost doubled, and the rectal temperature was slightly subnormal. The skin became dry and inelastic, with marked shedding of hairs. The salivary secretion ceased, and the oral and nasal mucosae formed dry incrustations. Death was attributed to starvation.

*Experimentally Produced Effects in Animals*—In addition to the work reported in the foregoing section on the changes in the blood, some further experiments with deficiency of water will be reviewed.

Engels (1904) showed by intravenous injections of physiologic sodium chloride solutions in dogs that the musculature, although forming only two fifths of the body by weight, absorbed about two thirds of the injected water. The skin absorbed about one sixth, the remaining sixth being distributed among the various organs. Skelton (1927), however, found that in cats, although the musculature absorbed the greater portion of the excess water when hypotonic solutions were used, it lost relatively little water when hypertonic solutions were injected. The skin, intestines and spleen, on the contrary, yielded water more readily during this dehydrating process.

Garofenu and Derevici (1924) studied the histologic changes in various organs of nine dogs on a dry diet for from four to nine days, with a maximal loss of 2,200 Gm (the initial weight being from 13 to 19 Kg). In the lungs, the alveoli appeared decreased in size, with some epithelial desquamation and extravasation of leukocytes and erythrocytes. In the kidneys, the glomerular capillaries were dilated, with cortical lesions in the advanced cases. The suprarenal cortical capillaries were less dilated than the medullary. The thyroid follicles were decreased and variable in size, the colloid and cytoplasm distinctly basophil. Granules of iron pigment appeared in the Kupffer cells of the liver, also in some other organs.

Some recent experiments on animals related to the aforementioned question of infantile toxicosis will now be reviewed. Various observers noted that hepatic lesions (fatty changes) usually result from a deficiency of water, and these lesions were held responsible for the toxic symptoms which follow (Finkelstein, Schiff and others). Schiff, Bayer and Chorenns (1925) studied the associated depletion of glycogen in

involved, resulting in a dehydration pyuria. Mild albuminuria, with variable casts, leukocytes and erythrocytes in the urine were noted. Renal abscesses may arise through bacteremia, the resistance of the kidneys being reduced by the injurious effects of the dehydration.

Aron (1926) reviewed the various effects of a deficiency of water in children. Water is held necessary for the removal of waste products, but chiefly for regulation of the heat in the body. Of all the organs, the brain suffers first, which accounts for the cerebral symptoms that occur during a deficiency of water. The kidneys also suffer, resulting in oliguria or even anuria, urinary casts and leukocytes. Pyelitis is aggravated. Various other symptoms were discussed.

*Effects on the Blood*—According to Marriott, the exhaustion of the water reserves of the body in infantile toxicosis is associated with marked anhydremia. The concentration of the blood is shown by refractometric determinations, and the reduction in total blood volume by Rowntree's method. The concentration and reduction of the blood cause circulatory disturbances, leading to decreased urinary secretion and disorders in various organs. Saxl and Donath (1924) concluded from experiments on rabbits that the reticulo-endothelial system plays an important rôle in regulating the water content of the blood.

Rosenbaum's observations and review of the literature confirmed, in general, the appearance of anhydremia, as indicated by the changes in water content, dry substances, serum albumin and viscosity, as well as in the erythrocyte count. In twenty-eight cases of infantile toxicosis, the increase in the erythrocyte count averaged 30 per cent, and ranged from 0 to 60 per cent. Some toxic cases did not show an increase, however, and some with (slowly rising) concentration of blood did not have any toxic symptoms.

In dogs subjected to thirst (method and details not given), Wetten-dorff (1899) found an increase in the number of red cells but a decrease in the number of leukocytes, hemoglobin content and density of the blood. In one dog subjected to "absolute inanition" for five days, the red cell count increased from 6,300,000 to 8,000,000.

Underhill and Roth (1922) observed that in rabbits complete deprivation of water led to an increase (up to about 25 per cent) in the concentration of the blood. After administration of water, the concentration of the blood rapidly fell to normal levels, as a rule, though in some cases death occurred in spite of the restoration of water. Keith (1924) produced a rapid dehydration of dogs without fatal results by the intravenous injection of saccharose or dextrose. From 7 to 10 per cent of the entire store of water was thereby excreted through diuresis within a few hours, without fatal results. The blood and circulation were rapidly restored to normal if an adequate amount of water was given within a few hours of the dehydration. Keith and Wheelan

by evaporation the average weight of the sciatic nerve decreased from 0.8439 Gm (75 per cent being water content) to 0.6693 Gm (51 per cent being water content)

Arager (1925) studied the development of frog tadpoles (*Rana temporaria*, *R. esculenta*) when the eggs were removed from water and placed in a moist chamber. Loss of water caused a marked reduction in the size of the body cavities, with displacement and deformity of the internal organs. However, the volumes of the organs and their histologic differentiation (studied especially in the eye) appeared nearly normal. Masses of mesenchymal tissue with normal nuclei formed thin strips between the organs.

De Almeida (1926) reviewed the literature on the effects of dehydration in amphibia, and reported original experiments. Rapid evaporation, he found, sometimes produced death in frogs that had suffered a loss of only 10 per cent in weight. The injurious effect he ascribed to the nervous system through abnormal cutaneous stimuli produced by the desiccation. When the evaporation was slower, the water lost from the skin was replaced from the deeper tissues. Under these circumstances, serious symptoms did not arise until there had been a loss of from 20 to 30 per cent in weight. Death from dehydration of the inner organs sometimes did not occur until there had been a loss of 40 per cent in body weight.

Some experiments have also been made on earthworms. Schmidt (1918) observed that when earthworms (*Allolobophora fetida*) were dried slowly, they might survive a loss of 61.6 per cent in weight, or nearly 73 per cent of their water content. In most cases, the blood vessels in the dried skin became ruptured, which caused death. Adolph and Adolph (1925) studied the changes in the water content of the frog, flatworm and earthworm (*Lumbricus terrestris*) under various conditions. In the same species of earthworm, Jackson (1926) found survival possible only up to a maximal loss of 43 per cent in weight. Measurements of areas viewed in cross sections indicated that during exsiccation in the earlier stages the epidermis, body muscles, celomic cavity, intestinal wall and lumen had lost, roughly, in proportion to their size. But, in extreme exsiccation, a relatively larger proportion of the loss had been contributed by the celomic cavity and the intestinal lumen. The loss in the tissues appeared to be chiefly from the intercellular spaces, as the cells (except those in the epidermis) showed but slight changes in size and structure.

*Effects in Plants*—The effects of a deficiency of water on growth and structure are especially evident in plants as was shown by Folsom (1918) for various species of the crowfoot (*Ranunculus*). Some of the tests were carried to the second and third generations, but an

the liver in puppies on a dry milk diet. When protein was added to this diet, both fatty changes and depletion of the glycogen of the liver resulted. But neither of these hepatic changes occurred in animals on the dry diet without protein. They therefore concluded that the changes in the liver are produced, not by the exsiccosis, but by the associated disturbances in intermediary protein metabolism. According to Schiff and Choremis (1926), disturbances in the carbohydrate metabolism are also evident under these conditions.

Kramar (1926) did not find symptoms of toxicosis in litters on a diet of condensed milk, although there was a decrease in weight, a concentration of the blood serum, wrinkling of the skin and great weakness. In puppies, however, the symptoms were more pronounced and closely resembled infantile toxicosis with loss of weight, nervous phenomena (with final coma), vomiting and diarrhea, leukocytosis, renal symptoms (glycosuria, albuminuria, cylinduria), hyperglycemia, thickening of the blood, deep breathing, acidosis, and other familiar appearances.

Kramar (1927), using puppies with concentrated milk diets of varied protein content, concluded (as did Schiff and others) that dehydration does not produce toxic symptoms unless there is a large proportion of protein in the diet. The protein-rich diet also produced a greater degree of dehydration, in spite of the fact that it contained a higher percentage of water than did the dry diet containing little protein. Protein is therefore of importance in producing the exsiccosis, as well as the subsequent toxic symptoms.

The pathologic changes produced by the dry diets (with high and with low content of protein) in puppies were described in detail by Kramar and Kovacs (1927). The liver was enlarged and light-brownish. Microscopically, there appeared marked hyperemia and fatty infiltration of the parenchymal cells. The fatty liver occurred in connection with a low content of protein as well as a high content of protein in the diets (which is contrary to the observations made by Schiff). The lesions of the kidneys were more irregular and inconstant, with both types of dry diets. Hyperemia was most pronounced among the straight tubules, while fat granules appeared chiefly in the convoluted tubules. Gastro-intestinal lesions (hyperemic or hemorrhagic spots in the mucosa) were inconstant, appearing only when the toxic condition was superimposed on intestinal disturbances. Ulcers rarely occurred. These lesions were found in connection with each type of dry diet and were therefore produced by the exsiccosis without reference to the protein.

The aforementioned experiments all had to do with a deficiency of water in mammals. Some studies have also been made on amphibia. Durig (1902) noted that in frogs losing 32.6 per cent in body weight

## Notes and News

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**University News, Promotions, Resignations and Appointments**—R Kraus, director of the State Serotherapeutic Institute in Vienna, has been appointed director of Instituto Bacteriologico de Chile in Santiago

Allen K Krause, associate professor of medicine and director of Kenneth Dows Tuberculosis Research Laboratory of the Johns Hopkins University, has been selected as director of the Desert Sanitarium and Research Institute near Tucson, Ariz

Emmerick von Haan of the University of Vienna has been appointed associate professor of pathology in the University of Arkansas, Little Rock

In the school of medicine of the University of Louisville, Ky, George McLean Lawson has been appointed professor of bacteriology

Charles L Connor, formerly instructor in pathology in Harvard Medical School, is now associate professor of pathology and executive head of the department in the University of California Medical School

Albert P Krueger of the department of bacteriology and experimental pathology in Stanford University has been appointed associate in the division of general physiology of the Rockefeller Institute for Medical Research

William B Wherry, professor of bacteriology and hygiene in the University of Cincinnati, is spending one year as visiting professor in preventive medicine in the University of Philippines

John A Kolmer, Philadelphia, has been awarded the Mendel medal by Villa Nova College for his work on immunology

At the University of Chicago, Harriet F Holmes has been appointed research associate in the department of pathology, and Milton T Hanke has been promoted to associate professor of biochemistry in the same department

On the occasion of the dedication of a new laboratory for anatomy and physiologic chemistry the degree of doctor of science was conferred on Simon Flexner by the University of Pennsylvania, where Dr Flexner was professor of pathology from 1899 to 1903

Howard M Jameson, Harding, Mass, has been appointed pathologist to the Decatur and Macon County Hospital, Decatur, Ill

J Forest Huddleson, Michigan State College, East Lansing, has been directed by the U S Public Health Service to carry on field investigations of undulant fever in various parts of Europe and Northern Africa

Clarence Cook Little, formerly president of the University of Michigan, is now director of the Jackson Laboratory for Cancer Research on Mount Desert Island, Me The investigations are to be conducted from a broad, biologic point of view

The Paris Academy of Medicine has awarded the Prince of Monaco prize of 100,000 francs to Professor Borel of Strasbourg for his work on the etiology of cancer

**United States Civil Service Examination for Bacteriologist**—An examination will be held to fill a vacancy in the United States Public Health Service, Honolulu The entrance salary is \$4,000 a year The duties are bacteriologic investigations and research in the field of public health Applicants will not be required to report for examination at any place, but will be rated on education, training, experience and fitness, and on publications or theses Applications must be on file with the Civil Service Commission, Washington, not later than July 3 next

**American Association of Immunologists**—At its recent annual meeting the American Association of Immunologists elected officers as follows president, Oswald T Avery, secretary-treasurer, A F Coca, and councilor, S Bayne-Jones

inheritance of the acquired characters was not observed. Fritsch (1922) and Fritsch and Haines (1923) similarly studied the changes produced by drought in various species of terrestrial algae. Rubner (1924) found that the growth of yeasts was markedly inhibited by dehydration in a 2 per cent solution of sodium chloride, although fermentation persisted up to concentrations beyond 4 per cent. The relations of dehydration to colloidal chemistry in growth and metabolism were discussed. A detailed review of the literature on the chemical and physiologic aspects was given by Palladin (1926).

*(To be Continued)*

LORDOSIS AS A CAUSE OF POSTURAL ALBUMINURIA M LEWISON, E B FREILICH and O B RAGINS, Arch Int Med **42** 440, 1928

Of twenty-five children with exaggerated lordosis, three showed a persistent tendency toward orthostatic albuminuria, and three others showed the tendency inconstantly. Alkalinization of the urine had no particular influence on the secretion of albumin. The chemistry of the blood showed no essential deviation from normal. It is concluded that lordosis is not an important factor in the production of orthostatic albuminuria.

H R FISHBACK

THE PARATHYROID GLANDS THEIR RELATIONSHIP TO THE THYROID, WITH SPECIAL REFERENCE TO HYPERTHYROIDISM E P McCULLAGH, Arch Int Med **42** 546, 1928

A review is given of the functional relationship of the thyroid and parathyroid glands, especially under abnormal conditions.

More than 550 determinations have been made of serum calcium in patients with thyroid disease, before operation, after ligation of the arteries and after removal of the thyroid gland. In 51 per cent of all cases there was a hypercalcemia distributed evenly in hypothyroidism and in hyperthyroidism. Hypocalcemia occurred in 1 per cent of all cases, and in each instance it occurred in a patient convalescing from thyroidectomy. In 75 per cent of the cases in which comparison was made there was an average post-thyroidectomy drop of 1 mg of serum calcium. This is considered due to operative trauma to the parathyroids, or to removal of parathyroid tissue.

H R FISHBACK

THE PANCREATIC ACTIVITY IN DIABETES MELLITUS S OKADA, T IMAZU, K KURAMOTHI, K HORIUCHI and T TZUKAHARA, Arch Int Med **42** 560, 1928

In a series of twenty-one cases of diabetes mellitus the external secretory efficiency of the pancreas was determined by the authors' new method. The disturbance of external secretion does not run parallel with the severity of diabetes. Amylolytic activity was reduced in one third of the cases, while proteolytic and lipolytic efficiency were decreased in over one-half. The activity of the pancreatic juice, as well as its volume, varies considerably. Nearly all old patients showed some enzyme deficiency.

H R FISHBACK

COMPARATIVE EFFECTS OF IODIDE AND OTHER SALTS ON WEIGHT AND GROWTH OF THE BODY P J HANZLIK, E P TALBOT and E E GIBSON, Arch Int Med **42** 579, 1928

Separate groups of rats were given complete and deficient diets, with the addition to the food of either sodium iodide, sodium sulphocyanate, sodium bromide, arsenic in solution of potassium arsenite, manganese sulphate, sodium borate or thallium acetate. The time periods extended from five to twenty-one months. The results are expressed in weight curves. The food consumption is also given. In both the adequate and the deficient dietary groups iodide gave some increase of weight and growth in the majority of animals. Reduction of weight and growth, or even death in some instances, was caused by the remaining salts given. Reduction in the amount of food consumed is believed to explain the weight loss in some groups.

H R FISHBACK

EXPERIMENTAL OBSTRUCTIVE JAUNDICE W C BUCHBINDER, Arch Int Med **42** 743, 1928

Jaundice was produced in puppies by ligation and division of the common bile ducts. The heart rate slowed rapidly in the first five days, and then more gradually for the next ten or fifteen days, after which there was an acceleration of

# Abstracts from Current Literature

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## Experimental Pathology and Pathologic Physiology

RENAL FUNCTION IN ARTERIAL HYPERTENSION RALPH H MAJOR, Am J M Sc **176** 637, 1928

Observations indicate that many patients with a hypertensive condition, belonging to the group called "essential hypertension," do not, as commonly stated, have normal function of the kidney. They are unable to excrete normally two guanidine compounds—methylguanidine and methylguanidine acetic acid anhydride (creatinine).

PEARL ZEEK

COMPOSITE CURVES OF CARDIOVASCULAR REACTIONS FOLLOWING ADRENALIN INJECTIONS IN TUBERCULOSIS PATIENTS GEORGE E DE TRANA and JOHN G HILLEBRAND, Am Rev Tuberc **18** 626, 1928

Composite blood pressure curves of patients with tuberculosis following the subcutaneous injection of 0.5 cc of 1:1,000 epinephrine indicate: (1) Minimal, moderately advanced and greatly advanced cases have, in general, vagotonic reactions. (2) Recovery from the effect takes place within an hour in the minimal and moderately advanced cases, while the greatly advanced cases show a prolonged effect. (3) The pulse rate in the minimal case is affected least, that in the moderately advanced group most. The extremely advanced cases show a primary slowing of the rate (vagtomic). (4) The curves of the cardiac output are not characteristic. When arranged on the basis of the weight curves, patients that are gaining show a primary sympatheticotonic reaction, and the systolic blood pressure of those in the stationary and losing groups remains level or diminishes, the pulse rate of patients in the losing group shows the greatest increase.

H J CORPER

MASSIVE COLLAPSE OF THE LUNG L SANTE, Ann Surg **88** 161, 1928

The author believes that this condition results from the simultaneous inhibition of the cough reflex by toxic or reflex stimulus, and that this permits secretion to accumulate in the bronchi. Both factors must be present. The various theories, the clinical signs and the treatment are presented.

N ENZER

EDEMA AND REDUCTION IN EXCRETION OF WATER IN PERNICIOUS ANEMIA E MEULENGRACHT, POUL IVERSEN and F NAKAZAWA, Arch Int Med **42** 425, 1928

Edema in pernicious anemia disappears during the remissions. Occult edema may be tested for by applying a tight rubber band about the extremity for two minutes. On removal, a positive test is indicated by a depressed groove in the skin. Accompanying the edema during relapses is a reduction of water excretion, as compared with normal, after giving a single large amount. The specific gravity of the hourly specimens of urine of the water test tends to remain fixed at a rather high level. Physicochemical examination of the blood in pernicious anemia reveals in many cases a decrease of the total protein of the plasma, with a proportional decrease of the colloid osmotic pressure. Some of the determinations of colloid osmotic pressure fell within the critical zone of from 270 to 240 mm of water, as applied to the appearance of edema in cases of nephrosis. The decreased hemoglobin itself is not a factor in the abnormal water metabolism, as proved in eleven cases of posthemorrhagic anemia with no edema and normal excretion in the water test. Renal function seemed to be good in a series of thirty-four cases of pernicious anemia, as tested by the blood urea, thiosulphate test and by urinalysis for albumin and casts.

H R FISHBACK



composition on a ration highly deficient in the vitamin B complex. The essential vitamin appears to be manufactured within the rumen as the result of the proliferation of a micro-organism of the genus *Flavobacterium*. Highly potent preparations of vitamin B can also be secured from this organism, in vitro, after culture on a synthetic medium.

ARTHUR LOCKE

CUTANEOUS AND VENOUS BLOOD SUGAR CURVES IN NORMAL INDIVIDUALS AFTER INSULIN AND IN LIVER DISEASE. M. FRIEDENSON, M. ROSENBAUM, E. THAUHEIMER and J. PETERS, *J. Biol. Chem.* **80** 269, 1928.

The influence of the administration of carbohydrates and of insulin on the relative concentrations of dextrose in the arterial and the venous blood is discussed.

ARTHUR LOCKE

MIXEDEMA FOLLOWING TREATED AND UNTREATED THYROTOXICOSIS. W. O. THOMPSON and P. K. THOMPSON, *J. Clin. Investigation* **6** 347, 1928.

An analysis has been made of the cases of thyroid intoxication associated with myxedema from the Thyroid Clinic of the Massachusetts General Hospital. Of the cases in which treatment was given, myxedema developed in less than 1 per cent following operation, and in about 4 per cent following roentgen therapy. With roentgen treatment myxedema developed as late as five years after treatment. Myxedema may also occur without any treatment. Many patients show low metabolic rates without myxedema. Thyroid therapy in cases of myxedema should be stopped for test periods, to prove whether or not the condition is permanent.

H. R. FISHBACK

THE VOLUME OF URINE AND THE RATE OF EXCRETION OF UREA BY NORMAL ADULTS. E. MOLLER, J. F. MCINTOSH, D. D. VAN SLIKE and E. M. MACKEY, *J. Clin. Investigation* **6** 427, 467, 485 and 505, 1928.

Blood and urine urea values and the volume of urine excreted hourly in six normal adults furnished data for determining the rate of the excretion of urea in relation to its concentration in the blood. Below a certain minute volume of urine, about 2 cc, the "augmentation limit," the excretion of urea falls at a rate proportional to the square root of the volume. About the augmentation limit, the excretion of urea is directly proportional to its concentration in the blood, and its minute-output represents the urea content of a maximum blood volume. This blood volume is termed the "maximum clearance," with an average value of about 75 cc. The "standard clearance" is the blood volume containing the excretion of urea for one minute, with the volume of urine for one minute at 1 cc. The mean value is 54 cc.

The urea values have been determined in normal children and compared with those for adults. The ratios for size are expressed in terms of body surface. The mean surface area of adults, aged 25, is taken as 1.73 square meters. Excretion of urea is found to vary directly as the surface area. When thus corrected, data for children give the same normal values as those for adults for the augmentation limit, and for maximum and standard clearances. In persons, between 62 and 71 inches (1.57—1.80 meters) in height, the correction for body size does not exceed 5 per cent in the determination of standard clearance.

The urea values have been determined in a number of patients with nephritis. The curves showing the excretion of urea are generally found to be lower than normal curves. This factor, as well as the blood urea value, must be considered in determining the extent of damage in a diseased kidney. The loss of renal function may exceed 60 per cent before the blood urea reaches even a high normal level. The standard clearance and maximum clearance were equally sensitive as indicators of damaged renal function in patients with nephritis.

The urea values were determined in normal persons and patients with nephritis at intervals throughout the day. The normal persons show a sharp drop in the

the rate. The heart rate of the puppies used as controls slowed as a result of age and growth until finally their rates averaged lower than those of the jaundiced puppies. Adult jaundiced dogs were more toxic than the puppies and exhibited an increase of heart rate. The initial bradycardia of jaundiced puppies may be vagal, the initial visceral sensory stimulus arising in the distended bile ducts. In decerebrate frogs sudden changes in pressure in the bile tracts cause a slowing of the heart rate. The central nervous depression occurring late does not play a part in slowing the pulse, since acceleration is the rule in the late periods. The inversion of the T wave in the electrocardiogram of jaundiced puppies may have a functional rather than an organic basis.

H. R. FISHBACK

ROENTGEN-RAY THERAPY OF THE HYPOPHYSIS IN A PATIENT WITH ACROMEGALY. R. E. AILLA and H. LISSER, *Arch Int Med* **42** 703, 1928

Roentgen therapy was administered to a patient with acromegalic bony deformities, adiposity, decreased sugar tolerance and headaches, polydipsia and polyuria. With antidiabetic dietary measures alone, symptoms improved, the patient lost weight and the blood sugar was kept within normal limits, although the sugar tolerance was not benefited. With roentgen treatment there was an improvement of sugar tolerance, and later a lowering of the slightly elevated basal metabolic rate.

H. R. FISHBACK

SECRETIN NOT A HEMATOPOIETIC STIMULANT. J. T. KING, *Arch Int Med* **42** 762, 1928

Four rabbits given injections of secretin over a period of eight weeks showed no increase in red blood cells over four control rabbits. Secretin as ordinarily prepared contains, among other things, proteoses, peptones and histamine, any of which may cause a sudden transient rise of erythrocytes by concentration. Analysis of some data in the literature indicates the importance, in blood changes in rabbits, of considering the normal cycle of red blood cells of from around 4,000,000 to 7,000,000.

H. R. FISHBACK

LACTOSE METABOLISM IN WOMEN. O. WATKINS, *J Biol Chem* **80** 33, 1928

During the last stages of pregnancy there is a more or less constant excretion of small amounts of lactose. During the last few days before delivery there is a sudden marked rise in the excretion of lactose, which reaches its height on the day of delivery. After delivery, the lactose excretion immediately drops to a low level where it remains for from two to five days. There is then a sudden and often tremendous excretion of lactose and, during the first few weeks of lactation, the fluctuations in the excretion of lactose are very marked. By the end of the first month after delivery the lactose excretion has assumed a constant and lower level, and this level slowly approaches the normal values for residual reduction of the urine as lactation progresses. The tolerance for lactose of most normal women is, in the intermenstrual period, the same as that of normal men, the tolerance dose being 10 Gm. Menstruation causes an increase in the tolerance of women for lactose, so that at this time many women show no urinary response to the ingestion of 20 Gm of lactose. During pregnancy the tolerance for lactose is increased, being in some women three times as high as in other persons. Also the urinary response to the ingestion of lactose is slower in pregnant women, and the return to normal is correspondingly slow. During lactation the tolerance for lactose is apparently the same in every way as it is in normal men and in most women in the intermenstrual period.

AUTHOR'S SUMMARY

SYNTHESIS OF VITAMIN B IN THE RUMEN OF THE COW. S. BECHDEL, H. HONEYWELL, R. DUTCHER and M. KNUTSEN, *J Biol Chem* **80** 231, 1928

Cattle, unlike the majority of the animal species, have the ability to grow to maturity, to produce normal offspring, and to produce milk of normal dietary

PHOSPHORUS POISONING AND THE ACTION OF INSULIN IN ANIMALS H J ARNDT and E GREILING, *Virchows Arch f path Anat* **67** 243, 1928

In rabbits, neither insulin nor sugar alone prevented the characteristic changes of phosphorus poisoning: fatty degeneration of the liver and loss of glycogen from the liver and muscles. With insulin and sugar together, fatty degeneration was not observed after phosphorus poisoning, and formation of glycogen took place in the liver, however, death of the animals was not prevented. Hence, the power of the liver to form glycogen, though reduced, is not entirely lost in phosphorus poisoning. The formation of glycogen in the renal epithelium did not occur, with or without insulin. The heart muscle appeared to be protected from loss of glycogen more than the skeletal muscle. No change in blood fat or cholesterol was observed, there were only inconstant changes in the lipoids of the suprarenal glands.

B R LOVET

EFFECT OF EXCISION OF THE ADRENAL GLANDS ON THE OVARIES IN MICE KIYOSHI MASUI, *Endokrinologie* **2** 49, 1928

In ninety-three mice the adrenals were removed, in seventy-one totally. The animals survived the operation on the average of six days. The mice that lived longer than twelve days regained their weight promptly, and all symptoms following the removal of the adrenals disappeared again.

The mortality rate was 73.3 per cent in the animals operated on previous to the sexual maturity, but only 52.3 in those after maturity. Mice in which regenerated adrenal tissue was found did not show symptoms, or only for a short time.

In some of the animals on which operations were performed accessory adrenals were found, which consisted only of cortical substance. Those animals did not show any nutritional disturbance.

The complete removal of the adrenal glands is followed in mice by a marked atrophy of the ovaries. The ova are degenerated, the interstitial tissue is hyperplastic and the formation of fresh corpora lutea ceases. A secondary atrophy of the endometrium of the uterus is observed.

These changes can be recognized seven days after operation and are maximal after from ten to fourteen days. Later, the ovary returns to normal. Masui believes that the atrophy of the ovary is caused by lack of the internal secretion of the adrenal glands, not by nutritional disturbances.

C A HELLWIG

### Pathologic Anatomy

EPIDERMOID CARCINOMA OF THE CERVIX UTERI KARI H MARTZLOFF, *Am J Obst & Gynec* **16** 578, 1928

Martzloff's study is based on seventy specimens of cancer of the cervix in which biopsy material was available for a later comparison with the remainder of the uterus. The author found that in one third of the cases studied a study of the biopsy material in carcinoma of the cervix failed to show the predominant type of cancer cell in the remainder of the organ. Therefore, studies of biopsy material merely for a determination of prognosis to the patient are more or less inaccurate.

T J KOBAR

THE DIAGNOSIS OF ENDEMIC YELLOW FEVER W H HOFFMANN, *Am J Trop Med* **8** 563, 1928

From our considerations the conclusion is drawn that the diagnosis of endemic yellow fever is not as easy as that of the severe epidemic form though the former is even more important as shown by the survey and control operations, which in the endemic centers always must be preceded by exact diagnostic work if they are to be effective, and an opinion on definite results of the hygienic measures can be formed only if the diagnostic service is based on completely reliable methods.

standard clearance after rising. There is a gradual rise during the late morning, followed by a drop during the early afternoon, and a second rise during the late afternoon and evening. The patients with nephritis give marked and irregular variation of the standard clearance curves. The period of least variation of values is during the forenoon, the taking of breakfast has no effect.

H. R. FISHBACK

THE MECHANISM OF THE INFLAMMATORY PROCESS (ELECTROPHORETIC STUDIES) H. A. ABRAMSON, *J. General Physiol.* **11** 743, 1928

Quartz particles and certain other inert particles were found to move cataphoretically in certain soft gelatin gels with the same velocity as in the sol. The speed is a function of the true viscosity of the sol or of the gel, and the presence of gel structure does not affect it in the soft gels. It is proportional to the applied difference of potential. While in certain sols gelatin results in increased stiffness, with increase of apparent viscosity, this is not accompanied by a change in true viscosity, as measured by the application of high pressures, and it does not affect the migration rate. Red cells in these gels showed a marked difference in behavior, their migration rate is about twice that of the quartz particles, and their absolute velocity is slightly decreased by the presence of the gel. In stiffer or more concentrated gels, red cells, leukocytes and quartz particles all move with the same initial velocity. If mechanical softening of these gels is induced, the red cells presently assume their more rapid rate of movement. Since it has been previously shown that injured connective tissue is probably electropositive to the blood stream and since the cataphoretic velocity of the negatively charged leukocytes in serum and plasma is about 0.5 microns per second per volt per centimeter, there is a force which may explain leukocytic emigration through the gel structure of the capillary wall.

H. E. EGGERS

HIGH BLOOD UREA, NON-PROTEIN NITROGEN, CREATININE AND URIC ACID VALUES IN A CASE OF BRAIN TUMOR H. A. FREUND, *Warthin Ann.* Vol. 1927 p. 691

The presence of large amounts of nonprotein nitrogen and urea in the blood has been associated with advanced nephritis. In the case reported by Freund, a physician, aged 53, showed blood urea values varying from 247 to 402 mg per hundred cubic centimeters during a period of two weeks. The maximum blood uric acid value recorded was 21 mg per hundred cubic centimeters, while the highest blood creatinine value was 11 mg per hundred cubic centimeters. The urinary observations were not of the character of those found in acute nephritis. During the following month, all of the nitrogenous values gradually dropped to normal and remained so until the patient's death, three months after the repeated high nitrogenous values were recorded.

Autopsy revealed a cerebral fibrosarcoma. The kidneys showed no significant pathologic changes. The clinical sequence of events was entirely consistent with the symptomatology of a slowly infiltrating tumor of the brain.

WALTER M. SIMPSON

THE FUNCTION OF THE BLOOD LIQUOR BARRIER V. KAFKA, *Deutsche Ztschr. f. Nervenheil.* **105** 50, 1928

Kafka again writes of the barrier between blood and spinal fluid, contending that its anatomic site is not in the meninges or cortical blood vessels, but in the choroid plexus alone. He denies the theory that fluid is formed by simple dialysis. The permeability of the barrier is discussed in general, but the author admits that although its function is of greatest importance in the etiology and therapy of nervous and mental diseases, the exact function is unknown.

ROY GRINKER

of simultaneous or rather constantly successive tuberculous disease of two physiologically different organs, which possess, however, the embryonic relationship of descending from the same primary germ layer, the mesoderm. These two groups of organs show a more constant simultaneous involvement by tuberculosis than does any other group of organs except that of the intestines and larynx.

II J CORPLER

THE SCAPULAR OF THE CHINESE. H. D. KIRK, Arch Int Med **42** 508, 1928

Various observers have reported on the relative frequency of different scapular types. The scaphoid type shows a decreasing frequency in the older age periods. Either the scaphoid scapula is converted to another form with increasing age, or the scaphoid type is eliminated by death. Observations were made on 546 Chinese from 15 to 78 years of age. The scaphoid scapular type gradually decreased from 82.1 per cent at from 15 to 20 years of age to 15.4 per cent at the age of 60 or more, which is interpreted as indicating an increased mortality among persons with scaphoid scapulae. No relation was found between the type of scapula and the occurrence of syphilis or tuberculosis.

II R FISHBACK

EXPERIMENTAL ULCERATION OF THE ESOPHAGUS. J. FRIDLINWALD, M. FRIDMAN and W. F. ZIRN, Arch Int Med **42** 521, 1928

Traumatic ulcers were produced in dogs by removing portions of the wall of the esophagus through an esophagoscope. Both superficial and deep ulcers were rendered chronic by the administration of 7.5 cc. of 10 per cent hydrochloric acid through a tube four times daily. This could be continued for several months. Roentgen examination demonstrated defects in outline at the site of ulceration, or spasm. Large penetrating ulcers sometimes simulated diverticula. By esophagoscopy examination the ulcers could be studied directly. They frequently perforated because of the thinness of the wall in dogs. The uncomplicated ulcers healed quickly without distortion of the wall, and without the fixation which may occur in human beings.

II R FISHBACK

XANTHOMATOSIS AND THE RETICULO-ENDOTHELIAL SYSTEM. R. S. ROWLAND, Arch Int Med **42** 611, 1928

Xanthomatosis is a disorder of lipid metabolism manifested by the storage of lipoidal substances in the reticulo-endothelial system, and further, by a hyperplasia of that system. There may be associated destructive processes in the membranous bones, exophthalmos and diabetes insipidus (Christian's syndrome). The two cases presented, and twelve others collected from the literature, show a generalized visceral xanthomatosis of this type. A review of the literature indicates the manifold systemic disturbances that may occur with lipid imbalance, or lipid gout, namely, Niemann's and Gaucher's diseases, dwarfism, infantilism, dystrophia adiposogenitalis, diabetes insipidus or mellitus, and other disorders of the ductless glands, certain diseases of the kidney, some disorders of the liver, and various obscure tumors.

H R FISHBACK

GENERALIZED GRANULOMATOUS LYMPHADENITIS ASSOCIATED WITH DIFFUSE PROGRESSIVE FIBROSIS OF THE LUNGS. C. L. CONNOR, Arch Int Med **42** 822, 1928

A case is presented of a boy with general enlargement of lymph nodes, and progressive consolidation of the lungs, who died in thirty days. Tissues taken at autopsy showed progressive fibrosis of the lungs, moderately hyperplastic bone marrow, and in places in the lymph nodes a mixed cell picture resembling Hodgkin's disease.

H R FISHBACK

With great care and experience on the part of the responsible authorities it will often, in spite of all difficulties, be possible to make the clinical diagnosis in cases in which yellow fever is suspected if each case is especially examined for this condition until its nature is clear

As long as clinical methods are insufficient and bacteriologic methods do not exist, the anatomic diagnosis is decisive and should be made in all fatal cases in the endemic territory in which death is due to an infection suggestive of yellow fever, or in mild cases in the monkeys infected with the blood of patients suspected of having yellow fever. This is probably the quickest and most reliable way to prove the presence of endemic yellow fever in a doubtful area

#### AUTHOR'S SUMMARY

THE FATE OF THE TUBERCULOUS CAVITY FELIX BAUM, SOL MEBEL and ALLEN KANE, *Am Rev Tuberc* **18** 596, 1928

The allergic stage in which tuberculous cavities are formed may be determined by the shape of the cavities and by the thickness of their walls. The fate of the cavity depends on the stage of its formation. There may be two types of cavities formed in the second stage: one through caseation, called "sequestrum cavity," and the other formed through liquefaction-necrosis, called "concentric." The kind of tuberculosis resulting in liquefaction-necrosis is more readily absorbed. There is a difference between the healing and the repair of a cavity. The latter process occurs in the third stage, in which the cavity is collapsed and masked by a thickened pleura. Healing takes place in the first two stages by connective tissue replacing the destroyed parenchyma. It is believed possible that healing can occur through the regeneration of parenchyma. Infraclavicular cavities, because of their location and the stage in which they are usually formed, show a strong tendency to spontaneous healing.

H J CORPER

TUBERCULOUS ENTERITIS BENJAMIN GOLDBERG, HENRY C SWEANY and ROBERT W BROWN, *Am Rev Tuberc* **18** 744, 1928

The postmortem observations of gastro-intestinal changes in 230 patients who died from pulmonary tuberculosis are reported. Tuberculosis of the gastro-intestinal tract should be considered with relation to the lymphatic system. The early lesion may be different depending on the age, race and immunity of the host with a tendency to be more exudative in the young and nonimmune person. Although in a minority of cases the lesions are definitely exudative, showing only polymorphonuclears, lymphocytes and epithelioid cell infiltration, with no giant cells and few tubercles, most cases show a mixture of exudative and proliferative processes, so that a definite classification cannot be made on such a basis. Incipient lesions are found most frequently, first, in the lymphoid tissue above the ileocecal valve, secondly, in the cecum at the point where the food-current strikes the cecum, thirdly, on the margin of the ileocecal valve, and very rarely at isolated points in the ileum or colon. Concomitant diseases are not uncommon, some of which are related to the tuberculosis while others are not. Acute appendiceal lesions are important and should be studied carefully with the view of removal before perforation and fecal abscesses result.

H J CORPER

THE ASSOCIATION OF TUBERCULOUS LYMPHADENITIS AND GENITO-URINARY TUBERCULOSIS F J LUSSMANN, *Am Rev Tuberc* **19** 95, 1929

The practical conclusion is deduced that if in patients with pulmonary tuberculosis, especially in advanced stages, a tuberculous involvement of the external jugular vein group of lymph nodes or of the intercostal lymph nodes is found, special attention should be paid to the genito-urinary system, as it is probably already tuberculous or in danger of becoming so. From a theoretical and immunologic standpoint this offers also a demonstration of the interesting fact

were varying degrees of obstruction. Roentgen examination demonstrated filling defects in eight. In fourteen of seventeen cases the malignant condition was carcinoma, six of which were multiple, in two, lymphosarcomas, and one, lymphatic leukemia. Bargen believes that the development of polyposis and chronic ulcerative colitis increases the chances of malignancy.

N ENZER

BLOOD SUPPLY TO THE APPENDIX. H. KOSTER and M. WEINTROB, *Arch Surg* **17** 577, 1928

Gross' method of vascular injection was applied to 100 normal and pathologic appendixes. There was demonstrated seven primary branches of the appendicular artery, six of which divide into two encircling branches. These in turn divide into a smaller superficial layer and a larger deep layer. These layers anastomose each other. Anastomoses can be demonstrated in the meso-appendix.

N ENZER

THE EFFECT OF LIGHT ON BLOOD AND TISSUE CELLS. W. R. EARLE, J. ENPER. *Med* **48** 667 and 683, 1928

Observations were made on hanging drops of blood obtained from veins in the ears of rabbits and exposed to irradiation. It was found that the red cells began to swell after from fifteen to thirty minutes, and then lost their hemoglobin, sometimes gradually, sometimes with explosive rapidity, hemolysis being complete at the end of from 90 to 110 minutes. Some cells also showed coagulation. In blood diluted with Locke's solution, the cells became hemolyzed one at a time instead of all at once. Hemolysis occurred at the same rate with white light and with light from each of the following spectral zones: (a) from 430 to 550 microns, infra-red, (b) from 475 to 630 and 690 microns, infra-red, and (c) 600 microns, infra-red. Washed cells underwent the same process of degeneration. The presence of air was apparently necessary, since in flat preparations from which air was excluded, degeneration did not take place. Changes in the white cells became evident only when hemolysis of the erythrocytes was complete, suggesting that substances liberated from the latter might be responsible for the degeneration of the former.

In the presence of autogenous red cells, fibroblasts from the hearts of embryo chicks also underwent degeneration when exposed to light, in the course of from three to four hours. The cells showed first an increase in the refractive index, followed by massive formation of vacuoles and sometimes by coagulation. The same wave length zones were active as in the case of the red cells, but the rate of degeneration varied markedly with light from the different zones, being slower through the blue or red filters and more rapid through the green filter. The presence of red cells was apparently necessary for the reaction, as in their absence only slight degeneration could be found even after from twelve to twenty-four hours.

B. R. LOVETT

PRIMARY CARCINOMA OF THE FALLOPIAN TUBES ASSOCIATED WITH TUBERCULOSIS. WILLIAM P. CALLAHAN, FRANCES H. SCHILTZ and C. ALEXANDER HELLWIG, *Surg Gynec Obst* **48** 14, 1929

Primary carcinoma of the fallopian tubes has been reported in 196 cases. Tuberculosis occurs in 1 per cent of all gynecologic cases, but the combination of primary carcinoma of the tubes associated with tuberculosis of the tubes has been reported only six times, the authors' case making the seventh. Secondary carcinoma of the tubes associated with tuberculosis is also extremely rare. The pathologic diagnosis of primary carcinoma of the tubes associated with tuberculosis must not be confused with the atypical carcinoma-like proliferation which is so common in tuberculous salpingitis. Extreme care must be exercised in making a pathologic diagnosis, so as not to confuse some of the inflammatory processes occurring in carcinoma of the tubes with tuberculosis. The consensus

AGRANULOCYTOSIS (SCHULTZ) AND THE AGRANULOCYTIC SYMPTOM COMPLEX  
W C HUEPER, Arch Int Med **42** 893, 1928

The given description of agranulocytosis is from five observed cases, and from reports in the literature. Clinical features are sudden onset in a healthy person, or more insidious onset after a period of ill health, high continued fever with chills, high rate pulse of poor quality, sore throat with ulcers of the throat and mouth, and enlarged cervical lymph nodes, jaundice, diarrhea, indefinite bacterial indications in the throat and blood, and marked decrease of leukocytes, especially the granulocytes. Pathologically, the ulcerations of the mouth vary from superficial erosions to deep gangrenous processes involving the larynx and esophagus. Ulceration may be found elsewhere in the gastro-intestinal tract, and on the vulva, vagina and cervix. The lungs frequently have scattered small areas of consolidation. There is cloudy swelling. The lymph nodes and spleen are hyperplastic. Red marrow is present in the long bones. Various diseases with secondary agranulocytosis may resemble essential agranulocytosis (Schultz).

H R FISHBACK

TABES DORSALIS. PATHOLOGY AND PATHOGENESIS. GEORGE B. HASSIN, Arch Neurol & Psychiat **21** 311, 1929

The histologic changes in tabes dorsalis may be classified as degenerative and inflammatory. The degenerative changes involving the posterior columns and the arachnoid portion of the posterior roots are a primary process due to disturbed circulation of the tissue fluids in the spinal cord, especially in its posterior columns. The inflammatory changes occur in the dura and the pia-arachnoid, in which they provoke reactive phenomena. In the dura they occur as infiltrations with hematogenous elements and vascular changes typical of syphilis, in the arachnoid they appear as proliferation of the cells of the arachnoid (arachnoid or mesothelial cells). These are most likely what Richter designated as "granulation" cells. The arachnoid cells invade the perineural spaces, obstruct them, and thus interfere with the flow of cerebrospinal fluid from the subarachnoid space, indirectly causing phenomena of stasis in the spinal cord. The stasis results in rarefaction of spinal cord tissue and its ultimate sclerosis, which shows as islands of degeneration in the posterior columns. The pia-arachnoid phenomena are secondary to the distinctly inflammatory conditions of the dura and the epidural space, invading the subjacent structures, they result in the changes just mentioned. The strangulation phenomena of Obersteiner and Redlich, Nageotte, Richter and others are contributory but are not the main factors. Many clinical phenomena can be better understood on the basis of the epidural origin of tabes with involvement of the peripheral nerves in the epidural space. Future studies of tabes should be centered on the epidural space, including both the spinal and the periosteal dura, as well as on the spinal nerves before they leave the intervertebral foramina.

AUTHORS' SUMMARY

CHONDROMYXOSARCOMA OF THE SIXTH CERVICAL VERTEBRA. EDWARD A. SHARP and WILLIAM F. JACOBS, Arch Neurol & Psychiat **21** 381, 1929

A vertebral tumor of the type of a chondromyxosarcoma of the sixth cervical vertebra and intervertebral disk, which produced compression paraplegia with the clinical symptoms, at the onset, of amyotrophic lateral sclerosis was presented. The spinal cord showed marked flattening from pressure outside the dura but not any degeneration of any portions of the structure of the cord. Multiple metastases were present in the lungs which showed tumor masses of the same character as that found in the vertebra and spinal canal.

AUTHORS' SUMMARY

CHRONIC ULCERATIVE COLITIS ASSOCIATED WITH MALIGNANT DISEASE. J. A. BARGEN, Arch Surg **17** 561, 1928

From 1916 to 1927, twenty-three cases of chronic ulcerative colitis with symptoms of malignancy occurred at the Mayo Clinic. In twelve of the cases, there



STUDIES OF GOITER IN MUNICH HANS SPATZ, *Deutsches Arch f klin Med* **158** 257, 1928

Spatz examined fifty-two goiters and thirteen normal thyroid glands and compared the microscopic, chemical and biologic data with the clinical symptoms. He found a direct relation between the clinical course and the efficiency of the goiter tissue in feeding tadpoles. Most of the goiters contain more iodine than normal thyroid glands. Iodine medication greatly increases the iodine content of the goiter. In adolescent and recurrent goiter, an extremely low relative and absolute iodine content is found.

Portions of the same goiter which show a greater biologic efficiency than the rest are usually richer in iodine. The microscopic picture does not run parallel with the clinical course, biologic efficiency and iodine content. Only the primary and secondary exophthalmic goiter, except the toxic adenoma, has a typical structure, strong biologic efficiency and low iodine content. The histologic picture of goiter with moderate hyperthyroidism often resembles that of exophthalmic goiter, but it cannot be distinguished sometimes from simple goiter.

The amount of colloid is always small in severe exophthalmic goiter, but it does not run parallel with the clinical, biologic and chemical data. Various portions of a gland can show so much difference in microscopic picture and biologic efficiency that only the examination of the whole gland is of value.

C A HELLWIG

BONE MARROW CHANGES IN EXPERIMENTAL LEAD POISONING J SPERANSKY and R SULIANSKAJA, *Folia haemat* **36** 289, 1928

In chronic lead poisoning the authors found that the bone marrow in the poisoned guinea-pig shows erythropoietic and leukopoietic changes. When the animals are treated with doses ranging from 38 to 70 mg of lead per kilogram of weight, an increased number of erythroblasts and microblasts appear in the marrow. There also is a marked increase in the number of the young unripe cells, i e, macroblasts and proerythroblasts. In instances in which there is a pronounced erythropoietic reaction in the marrow, this is followed by an extra-medullary erythropoiesis (myeloid metaplasia of the spleen). There is a close relationship between the changes in the blood and those in the marrow. The authors were also able to notice that in normal guinea-pigs the morphology of the bone marrow is constant.

B M FRIED

A CASE OF LYMPHOGRANULOMATOSIS MALIGNA COMBINLED WITH TUBERCULOSIS K RUDSIT, *Folia haemat* **36** 358, 1928

Rudsit reports a case of a man, aged 50, who showed tuberculosis and Hodgkin's disease in the same glands. From a pathologic standpoint, there was a suggestion of an etiologic relationship between the two conditions. This case, therefore, would support the conception that malignant lymphoma is an "unusual" variety of tuberculosis. From a clinical point of view, the case is of interest in that it occurred in a person 50 years of age which is uncommon, the Pirquet test was negative on repeated examinations, there were symptoms referred to the brain. The history of the thoroughly studied case is given in detail.

B M FRIED

THE INTRAVASCULAR OCCURRENCE OF MEGACARYOCYTES IN MAN SVEND PETRI, *Folia haemat* **37** 129, 1928

In three thoroughly studied cases of leukemic myelo-adenosis Petri found megacaryocytes in the blood smear, and also in the tissues removed post mortem. In one instance these cells were present in the renal vessels and in another they were conspicuous in the pulmonary capillaries. The so-called granular mega-

of opinion regarding the etiology of these conditions is that the one is an accidental complication of the other, and although the tuberculous process is usually the older, it can not be proved that it is the cause of the carcinoma. One case was reported of a primary carcinoma of the right tube and tuberculosis of the left tube. The prognosis is unfavorable. Early radical operation is the only treatment which offers any success. After two years the authors' patient showed no metastases and was in good health, with the exception of the presence of a fistula.

AUTHORS' SUMMARY

INHERITED EPITHELIAL DEFECTS IN CATTLE F B HADLEY and L J COLE, Research Bulletin 86, Agricultural Experiment Station of University of Wisconsin, 1928

New-born calves exhibiting characteristic lesions of the skin and the mucous membrane were reported from a number of herds of Holstein-Friesian cattle in Wisconsin. The following lesions were characteristic: defective formation of the skin below the knees, one or more undeveloped claws, deformed ears, due to rolling of the margins and growing together of the surfaces brought into contact, indicating that the lesions antedated birth by some weeks, defects in the integument of the muzzle and in the mucous membrane of the nostrils, tongue, hard palate and cheeks. The defect does not appear to be associated in any way with faulty nutrition or with thyroid or other disturbances of the internal glands of the mother. Neither is it due to specific infection. The defect appears to be specific, and is designated *epitheliogenesis imperfecta neonatorum bovis*. The affected calves are carried to full term and are of normal size at birth. Some appear strong when born, others are weak and unable to stand, and all soon become debilitated and die even when given appropriate treatment and good care. Death is apparently attributable to a septicemia (blood poisoning) which develops as a result of infection gaining entrance to the body through the raw surfaces of the lesions. Studies of the microscopic changes revealed marked pathologic changes. Whether the epithelial structures had reached full development and then retrogressed, or whether the condition was due to incomplete or arrested development, is an open question. The latter conclusion appears the more probable. The method of inheritance of the epithelial defect indicates that it is due to the expression of a single recessive gene. This was borne out by experiment matings made for the special purpose of testing the matter. The conditions of the observations and experiments are such that good 3:1 ratios could not be obtained, but there is every indication that one is dealing with a simple monohybrid relationship. The allelomorphous normal gene is completely dominant, heterozygous dominants showing no visible evidence that they carry the defective heredity.

AUTHORS' SUMMARY

RUPTURE OF HEART FROM ABSCESS G H STEVENSON and A J MARSHALL, Glasgow M J 110 337, 1928

A boy, aged 9 years, died without warning from the rupture of the left ventricle through a myocardial abscess which had formed in the course of a pyemia of traumatic origin.

EXAMINATION OF BONE MARROW IN VIVO IN PERNICIOUS ANEMIA L FONTANA, Arch per le sc med 52 497, 1928

The marrow from the body of the sternum was examined in twelve typical, mostly severe, cases of pernicious anemia. Megaloblasts were found in practically all cases: in seven from 2 to 6 per cent and in five from 10 to 21 per cent of the nucleated cells were megaloblasts. In view of the almost invariable presence of megaloblasts in the marrow in pernicious anemia and their absence in most other forms of anemia, examination of the marrow may have considerable diagnostic value. There seems to be no definite relation between the megaloblasts in the marrow and megaloblasts in the blood.

PRIMARY BLOOD-FORMING HEMANGIO-ENDOTHELIOMA OF THE LIVER G  
ORZECOWSKI, Virchows Arch f path Anat **267** 63, 1928

Primary hemangio-endotheliomas of the liver are rare, malignant tumors, composed of endothelium, which attempts to perform its function of building blood vessels in the tumor mass. Two forms have been described, with and without formation of blood cells. In the author's case, tumor nodules were found throughout the liver, with newly formed blood vessels, and containing early forms of blood cells—myelocytes, metamyelocytes and nucleated red cells.

B R LOVETT

"BLOCKADE" OF THE RETICULO-ENDOTHELIAL SYSTEM G L DERMAN, Vir-  
chows Arch f path Anat **267** 73, 1928

The author states that, following intravenous injections of ferric oxydum saccharatum into normal dogs and rabbits, the iron is found almost entirely in the reticulo-endothelial cells, in the liver, spleen and bone marrow. After a moderate degree of blockade of the reticulo-endothelial system, through several daily injections of collargol, the faculty of these organs to absorb iron is reduced, especially in the bone marrow. A higher degree of blockade calls forth proliferative activity, and the power of taking up iron is thereby increased. Splenectomy is followed by degenerative and proliferative changes in the reticulo-endothelial tissue, and in the bone marrow by increased activity in taking up iron, both with and without the blockade. The activity of the cells of the liver in this respect depends on the character of the degenerative and proliferative changes in that organ.

B R LOVETT

RETICULOSIS AS A SYSTEMIC DISEASE OF THE BLOOD-FORMING ORGANS T  
TSCHISTOWITSCH and O BYKOWA, Virchows Arch f path Anat **267** 91,  
1928

An unusual disease of the hemopoietic organs is described, presenting an isolated increase in the reticulo-endothelial elements of various lymph nodes, the spleen and in part of the bone marrow. Numerous "reticulomas" were found in the liver. The authors regard this as the first pure case of aleukemic reticulo-endotheliosis.

B R LOVETT

SYSTEMIC DISEASE OF THE BONE MARROW F BATTAGLIA, Virchows Arch  
f path Anat **267** 106, 1928

The process in myeloma is almost similar to that in the myeloses, but it presents certain differences, chiefly the destruction of bone, and the fact that it remains confined to the skeleton. The growth of nodules in the skeleton as a differential point appears to the author to be of little significance, since, as in his case, this process may be scarcely indicated. Cases of myeloma occur with leukemic blood changes, as well as with aleukemia. The significant factor seems to be the growth of the original hyaloid cells. The composition in the different cases depends on the period of development in which the cells are arrested and the cell type toward which they are developing.

B R LOVETT

THE STRUCTURE OF ERYTHROCYTES M GUTSTEIN and G WALLBACH, Vir-  
chows Arch f path Anat **267** 144, 1928

Heinz, and later Ehrlich, described round bodies in the red cells, which appeared after treatment with a hemoglobin toxin, and which were presumably degeneration products containing methemoglobin. From a variety of staining reactions and the demonstration of the bodies without previous action of a toxin, the authors concluded that the bodies do not contain methemoglobin or any other hemoglobin degeneration product, and that their presence is not due to intoxication. They appear to be constituents of the normal red cell.

B R LOVETT

caryocytes contained red cells in their cytoplasm which he interprets as a phenomenon of phagocytosis. In no instance could he find what he calls "Wrightsche Figuren" whether in tissues or in dry smears, and he believes them to be artefacts. The article is from Fibiger's Institute and has a long list of references.

B M FRIED

**IODINE DEFICIENCY AND ENDEMIC GOITER** P SCHMITZ-MOORMANN and F MEIS, *Mitt a d Grenzgeb u Med u Chir* **41** 131, 1928

In dogs, excision of one and one half of the thyroid is followed by compensatory hyperplasia of the remaining thyroid tissue. Goitrous glands show cellular proliferation only after resection of more than one and one half of the gland. By the administration of iodine, postoperative hyperplasia of the thyroid can be prevented. These experiments prove that endemic goiter is a compensatory process dependent on a relative or absolute deficiency of iodine.

C A HELLWIG

**THE HYPERFUNCTION OF THE ISLANDS OF LANGERHANS IN DOGS** D E ALPERN and W P BESUGLOW, *Klin Wchnschr* **7** 586, 1928

The pancreatic duct was ligated, or a mass ligation was made through the tail of the pancreas. By these operations the external secretion of the gland was not completely interrupted and the digestion was not disturbed.

Changes resulted in the metabolism of carbohydrates, fats and mineral salts which were interpreted as the increased internal secretion of the pancreas and which resembled the changes seen after the injection of insulin. There was hypertrophy of the islands of Langerhans.

C A HELLWIG

**THE ORIGIN AND PRODUCTION OF RENAL CASTS** H VON HOESSLIN, *Klin Wchnschr* **7** 1893, 1928

A general review of the origin of renal casts is followed by a report of the structures formed in kidneys by maceration with hydrochloric acid and pepsin. Although epithelial and granular casts can be simulated by this method, the origin of hyaline casts is not so easily determined. Possibly they arise from slowly eliminated cell constituents. The origin of waxy casts is even more difficult to determine, but undoubtedly they also are derived from cell substance.

E F HIRSCH

**PATHOLOGY OF COLLAGENIC CONNECTIVE TISSUE FIBERS** S WAIL, *Virchows Arch f path Anat* **267** 1, 1928

Autopsies on two patients dying of sepsis revealed unusual changes in the collagenic fibers. These structures took the hematoxylin stain avidly, and presented a broken appearance, due to irregularity in staining. The pale central core of the fiber was surrounded at intervals by deeply stained rings. The same changes were produced in guinea-pigs by intraperitoneal injection of organisms from one of the human cases.

B R LOVETT

**AN ABNORMAL RIDGE IN THE LEFT VENTRICLE** L BRINGS and A SPITZER, *Virchows Arch f path Anat* **267** 9, 1928

At autopsy on an infant with congenital heart disease, a connective tissue ridge was found in the left ventricle, on the boundary between the muscular and the membranous portions of the septum. It extended also on to the aortic leaflet of the mitral valve. An explanation for the development of this anomaly is given.

B R LOVETT

SYMPATHETICOTROPIC CELLS IN THE OVARY L BERGER, Virchows Arch f path Anat **267** 433, 1928

Berger found the cells which he called "sympatheticotropic" 168 times in 218 pairs of ovaries. He denied the chromaffin nature of these cells (affirmed by Neumann), and found them similar in form and structure to the Leydig cells in the testis. Since they appeared to be of secretory nature and to bear some relation to the nervous mechanism of the organ, he referred to them as "neurocrine" structures.

B R LOVETT

THE ETIOLOGIC CONDITIONS FOR THE DESTRUCTION OF HARD PARTS B ORBAN and J WEINMANN, Virchows Arch f path Anat **267** 446, 1928

From studies on the teeth of rats, it appeared improbable that narrowing of a cavity through building up on one side could result in absorption on the other side. The fact that absorption of uncalcified substance proceeds more slowly than that of calcified material probably depends on different characteristics of the tissue in question.

B R LOVETT

LEUKEMIC RETICULO-ENDOTHELIOSIS B SWIRTSCHESKAJA, Virchows Arch f path Anat **267** 456, 1928

The author adds a case of monocytic leukemia to those already described in the literature. The clinical observations were those of a leukemia. The blood revealed from 50 to 96.2 per cent of cells of the monocytic type. At first they resembled adult monocytes, and later earlier forms of these cells, probably promonocytes. Histologically, there was found in the spleen atrophy of lymphoid tissue, areas of necrosis, increase in the connective tissue stroma, and changes in the sinus endothelium indicating a desquamation of endothelial cells, which subsequently multiplied in the blood and other organs. The case was, therefore, a monocytic leukemia, resting on hyperplasia of the reticulo-endothelial system, especially in the spleen, and to some extent in the liver and bone marrow. The author divides the cases in the literature into two groups: hyperplasia of the reticulo-endothelial system with relatively normal blood, and hyperplasia with monocytic blood, usually accompanied by myeloid hyperplasia in the bone marrow and elsewhere. His case suggests the possibility of the endothelial origin of the blood monocytes.

B R LOVETT

EXPERIMENTAL STORAGE OF FAT I MARGAT, Virchows Arch f path Anat **267** 477, 1928

Parenteral injection of lecithin in the form of an emulsion into guinea-pigs resulted in storage of the fat in the spleen, liver and lungs. This was more marked in tuberculous than in normal animals, not only in the region of tuberculous foci, but also in organs free from infection, such as the liver.

B R LOVETT

CONTRIBUTION TO THE KNOWLEDGE OF INFLAMMATION AND OF MONOCYTES M SILBERBERG, Virchows Arch f path Anat **267** 483, 1928

The first series of experiments on the effect of injections of benzene into rabbits showed that benzene acts as a selective toxin for the myeloid tissue, resulting in atrophy of the bone marrow and marked reduction of polymorphonuclear leukocytes in the blood, without much effect on the red cells or lymphocytes. In animals rendered nearly free from leukocytes in this way and exposed to septic infection, numerous necroses appeared in the organs, without inflammatory reaction or abscess formation. The macrophages were seen to be active. However, it was not observed that any other cells, particularly those of histogenic origin, could take the place of the missing blood leukocytes, which are of the greatest importance in combating septic infection.

LYMPH NODES IN ACUTE AND CHRONIC INFECTIONS M NORDMANN, Virchows Arch f path Anat **267** 158, 1928

Systematic examination of lymph nodes in man enabled the recognition of two types according to histologic structure (1) mesenteric and aortic nodes and (2) peripheral nodes (axillary and inguinal). The first type is characterized by prominence of the lymph sinus and marked development of the sinus endothelium. This depends on the large quantity of material for storage brought by the lymph stream, and is in relation to active metabolism in the adjacent organs. In the second type storage takes place in the reticulum of the lymphatic tissue without marked participation by the sinus. Storage of coal dust serves as an example. From these groups, one can deduce two general types of lymph node changes (1) nodes with feeble absorptive activity and storage in the reticulum of the lymphatic tissue and (2) nodes with strong absorptive activity and storage in the increased endothelial and reticulum cells of the sinus.

Corresponding to the normal, under pathologic conditions of greatly increased material for storage, marked growth of the sinus endothelium is found, "sinus catarrh." This condition corresponds, therefore, to pathologically heightened metabolism in the regional organs, and not to local inflammation, or lymphadenitis. Storage in lymph nodes depends on the lymph flow, and occurs where the flow is slowest, or even stagnant, that is, in the lymphatic tissue of weakly absorbing glands and in the sinus of strongly absorbing glands. The different conditions of lymph flow explain the differences between the medulla and cortex, and also the histologic structure of passively congested glands. Lymphovascular induration is the late stage of sinus catarrh, while reticular induration of the lymphatic tissue represents the end-stage in the glands of peripheral type. Acute inflammatory processes, hyperplasia, necroses and consequent induration do not rest on functional alterations in the lymph stream, but are related to changes in the blood channels. In lymph nodes in acute and chronic general infections, sinus catarrh, in its various stages, plays the chief part, beside the inflammatory and hyperplastic changes.

B R LOVETT

CELLULAR PROCESSES IN ATROPHY OF BONE P GUNKEI, Virchows Arch f path Anat **267** 204, 1928

Atrophic changes in bone are called forth by altered cell activity, and destruction takes place only through the cells, and not through chemical activity of the tissue fluids. All destructive cells (osteoclasts, etc.), and perhaps also the building cells, originate from the blood vessels. The change of blood vessels into destructive cells begins in the periosteum, haversian canals and medulla with congestion and growth of the adventitia. The histologic picture is fundamentally the same in all atrophies, and shows differences only in that the process in disease of the circulatory system is slower, while in cachexia the early development of destructive elements is more prominent. Formation of osteoblasts takes place at the same time, but is soon overshadowed by the destroying activity. Fibrous atrophy occurs only in severe cases, especially in disease of the organs of circulation.

B R LOVETT

MALFORMATIONS OF BOWMAN'S CAPSULE E RISAK, Virchows Arch f path Anat **267** 222, 1928

Risak observed that in the kidneys of a woman dying with pyelonephritis, the parietal layer of Bowman's capsule in many glomeruli was composed of cuboidal epithelium similar to that of the proximal convoluted tubules. In some glomeruli the visceral layer was also of this type, and in one the cells were high and cylindric. In all, the capillaries were plump and the loops few. Study of fetal and infantile kidneys revealed that in embryologic development, the capsule epithelium is first of cylindric or cuboidal type later becoming flattened. The author explains the abnormality in his case, not as a metamorphosis due to the chronic infection, but as a malformation due to arrested development.

B R LOVETT

In seventy-three autopsies, congenital pneumonia was present twenty-two times and pneumonia in the first few days of life fourteen times. The presence of pneumonic foci could be determined in many cases only with the microscope. Amniotic fluid or other constituents of the birth canal were found regularly in the lungs. The pneumonias were of bronchogenic origin, even the congenital cases, due to aspiration of infectious material, there was no evidence of blood infection through the placenta. Histologic examination of the lungs should be made more frequently in these infants, especially in those dying with signs of asphyxia.

B R LOVETT

ANEURYSM OF PLACENTAL ARTERY O HINTZE, *Ztschr f Gynak* **52** 2524, 1928

Hintze reports two cases. Above the aneurysm, which was as large as a cherry, there was, in each case, a sharp kink in the artery and in one case the artery ran a serpentine course in its entire length. The artery affected was in each case that which supplied the larger part of the placenta. The aneurysm lay below the anastomosis, which was by a ramus intermedius. Birth was spontaneous, in one case there was premature detachment of the placenta and the child was born asphyxiated. The origin of the aneurysms could not be explained. Syphilis was not present. Hintze suggests that in unexplained intra-uterine death, the possibility of rupture of an aneurysm of a placental artery should be remembered.

SPASTIC PSEUDOSCLEROSIS RICHARD ZIMMERMAN, *Ztschr f d ges Neurol u Psychiat* **116** 1, 1928

This seventh case of Jakob's disease revealed microscopically a diffuse and progressive process consisting of the complete disappearance of ganglion cells in small areas. The pyramidal cells either were sclerosed or revealed fatty and degenerative changes. The disease affected the entire cerebral cortex, especially the frontal and temporal lobes and motor cortex, although the basal ganglions were also much involved. It is interesting to note the author's attempt to correlate each clinical symptom with certain degenerated areas.

ROY GRINKER

A CEREBELLAR CYST COMPLICATED BY CHRONIC ARACHNOIDITIS L M GLAUBERMAN, *Ztschr f d ges Neurol u Psychiat* **116** 15, 1928

In a patient who had an apparently congenital cerebellar cyst without a tumor in its wall or any other possible explanation for its presence, a rather mild trauma caused the development of a serous meningitis. This resulted in the formation of a second encapsulated cyst in the posterior fossa cyst. Repeated lumbar punctures relieved symptoms of intracranial pressure caused by the serous meningitis but resulted in an aseptic purulent meningitis which caused death.

ROY GRINKER

BRAIN SWELLING SUZANNE ZINGG, *Ztschr f d ges Neurol u Psychiat* **116** 71, 1928

A condition diagnosed as cerebral tumor of undetermined localization revealed, on postmortem examination, only a swelling of the brain (Reichardt). The patient was a woman, aged 17, and the brain weighed 1,420 Gm, about 200 Gm overweight. No gross or microscopic cause for the increased weight could be found. The author therefore believes that the volume of the brain was greater than the capacity of the skull which, unfortunately, he neglected to measure.

ROY GRINKER

Experiments *in vitro*, with tissue from animals poisoned with benzene, revealed that the reticulo-endothelial system is entirely independent of the myeloid and lymphoid tissue, and is injured neither morphologically nor functionally by benzene. Derivation of monocytes from histiocytes could be shown *in vitro*, indicating the independence of these cells and their difference from the other blood cells. No transition between monocytes and lymphocytes or myeloid cells could be observed. In animals previously given injections with carmine particles so that the macrophages were "blocked," the course of infection was more severe than in control animals, and fewer organisms were taken up by the macrophages. The activity of the leukocytes was not impaired. The author believes in the independence and functional difference of the three types of white blood cells, leukocytes, lymphocytes and monocytes. Transition between the types, or derivation of one from another, is not possible in postembryonic life, although the three are embryologically derived from the same undifferentiated mesenchymal cell.

B R LOVETT

CLASSIFICATION OF ENDOCARDITIS H KRISCHNER, *Virchows Arch f path Anat* **265** 545, 1927

Krischner investigated seventy-eight cases of valvular disease at autopsy, and classified them according to the method of Beitzke. He distinguished simple or verrucous endocarditis and septic endocarditis, including polypous, ulcerative and mixed forms. In thirty-six cases of mixed endocarditis, thrombi were found only on the free borders of the leaflets not exceeding a pinhead in size. They were pale yellow or reddish and firmly adherent. Microscopically, the nodules consisted largely of blood platelets, without bacteria, fibrin or appreciable numbers of leukocytes. In rheumatic endocarditis, midway between the simple and septic types, the deposits were more extensive and larger, with cellular reaction extending into the substance of the leaflets, but with no serious anatomic defects resulting. Thirty-five cases of endocarditis polyposa showed depositions spreading beyond the border into the substance of the leaflets, and sometimes into the chordae tendinae. The nodules were larger than those observed in the simple form, reddish brown or reddish yellow, and either soft and friable or calcified. They consisted of a fibrinous network, containing leukocytes, red blood cells and bacteria, resembling a diphtheritic membrane. The leaflets were thickened, vascularized and sometimes revealed areas of necrosis surrounded by leukocytes. Only one instance of the ulcerative form was found. The cases of endocarditis simplex corresponded to a reparative inflammation, endocarditis rheumatica to a productive, and endocarditis polyposa or ulcerosa to a fibrinopurulent type.

B R LOVETT

THE ORIGIN OF LEUKOCYTES IN ACUTE INFLAMMATORY EXUDATES W GERLACH and A JORES, *Virchows Arch f path Anat* **267** 551, 1928

Mollendorff's experiments on the excised jugular veins of guinea-pigs were repeated. Various irritants failed to produce any changes in the vessel walls or surrounding tissue suggestive of local formation of leukocytes from these tissues. Further experiments on animals rendered aleukocytic by means of injections of benzene failed to show evidence of local formation of leukocytes in response to irritants. All results indicated the blood stream, and originally the bone marrow, as the sole source of leukocytes in acute inflammatory reactions.

B R LOVETT

CONGENITAL NONSPECIFIC PNEUMONIA AND PNEUMONIA FROM ASPIRATION IN THE BIRTH PASSAGES H HOOK and K KATZ, *Virchows Arch f path Anat* **267** 571, 1928

In an investigation of stillbirths and infants dying in the first few days of life nonspecific aspiration pneumonia was found to be a frequent cause of death.



A COMPARISON OF THE THRESHOLDS OF KETOSIS IN DIABETES, EPILEPSY AND OBESITY W S McCLELLAN, H J SPENCER, E A FALK and E F DU BOIS, *J Biol Chem* **80** 639, 1928

The threshold of ketosis is defined as the fatty acid dextrose ratio characterizing the food being metabolized at the moment when an abnormal concentration of acetone substances first becomes apparent in the urine. Studies of six men—three of them normal, one epileptic, one diabetic and one obese—indicate that while the threshold may be reached normally at ratios of 1:15, it may be somewhat higher in diabetes and epilepsy and considerably higher in obesity.

ARTHUR LOCKE

CHANGES IN THE RATE OF EXCRETION OF ACETONE BODIES DURING THE TWENTY-FOUR HOURS W S McCLELLAN and V TOSCANI, *J Biol Chem* **80** 653, 1928

In persons manifesting ketosis, acetone substances appear in the urine in greatest concentration during the later afternoon and night.

ARTHUR LOCKE

BILE SALT METABOLISM G H WHIPPLE and H P SMITH, *J Biol Chem* **80** 659, 671, 685 and 697, 1928

Neither cholesterol, yeast nucleic acid nor the alcoholic extractives of meat tissue appear to influence the rate of synthesis and secretion of the biliary acids. The contrasted, marked acceleration produced following the ingestion of whole meats and such meat derivatives as retain a moiety of protein suggests that the biliary acids are synthesized from products of protein disintegration rather than from lipid and cholesterol, as has been assumed.

ARTHUR LOCKE

BIOMETRY OF CALCIUM, INORGANIC PHOSPHORUS, CHOLESTEROL, AND LIPOID PHOSPHORUS IN THE BLOOD OF RABBITS ALVIN R HARNES, *J Exper Med* **49** 287, 1929

A series of determinations of inorganic phosphorus, calcium, cholesterol and lecithin were made on a group of ten animals living in the laboratory from Oct 27, 1927, to May 17, 1928. A marked difference in both the trend and the absolute values was noted in animals living in the laboratory when compared with the values obtained for animals living out-of-doors. With animals living in the open, the trend of variation for calcium was found to be the same. However, animals living in the laboratory maintained a higher level over the same period of time. The inorganic phosphorus and lecithin both showed a marked decrease and both maintained a lower level than was found in animals just received from the dealer. The cholesterol content of whole blood exhibited a similar trend in both groups of animals. However, it was found that animals living in the laboratory maintained a lower level than animals living out-of-doors. The mean value for calcium was found to be  $157 \pm 0.05$  and for inorganic phosphorus  $4.65 \pm 0.05$  mg per hundred cubic centimeters of blood serum, and for cholesterol  $58.2 \pm 0.39$  and for lecithin  $118.4 \pm 1.13$  mg per hundred cubic centimeters of whole blood. The coefficients of correlation having the highest degree of mathematical significance were obtained from the mean values for individual animals.

AUTHOR'S SUMMARY

MELANOTIC PIGMENTS R L MAYER, *Klin Wchnschr* **7** 2471, 1928

The precursors of the pigment in melanin-producing cells, oxidized to quinones from substances such as tyrosin, epinephrine, etc., combine with cell protein to form the melanins. The melanin pigment therefore consists of a quinone and a combined protein group. Both may vary in composition. Lipoids or lipid-like substances may participate in the second group.

EDWIN F HIRSCH

INFECTIOUS TOXIC MYELITIS WITH DESTRUCTION OF THE SPINAL CORD J  
SILBERMANN, *Ztschr f d ges Neurol u Psychiat* **116** 140, 1928

Many acute infectious diseases have caused severe damage to the spinal cord which has been attributed to the action of a toxin, to the actual invasion of the cord by bacteria or to an involvement of the vascular system, secondarily affecting the cord. Trauma and syphilis have also been ascribed roles as predisposing factors. The case reported had three contributing factors in that the patient, of syphilitic parents, fell on his back and developed a severe angina and gingivitis at the same time. Severe symptoms developed in the spinal cord a week later. At postmortem examination, one and one-half years after the injury, the entire lumbosacral cord was found destroyed without a trace of the normal nerve fibers. In the dorsal and cervical regions, added to the ascending secondary degeneration there were many small areas of softening. No definite decision was made as to the primary cause.

ROY GRINKER

THE PATHOLOGY OF BRONCHIAL ASTHMA HILDING BERGSTRAND, *Acta path et microbiol Scandnav* **5** 251, 1928

The results of the postmortem examination in two cases of bronchial asthma are described. The changes were not such as usually are caused by bacteria but are regarded rather as expressions of a general allergy at the same time as the asthma which in both the cases probably resulted from respiratory infection. The bronchi did not contain any exudate but the products of secretion of a hyperplastic lining, the epithelium cells of which were changed into goblet cells. The inflammatory fossae in the lungs were not characteristic of bronchitis or pneumonia but resembled in part the changes that result in the skin on the reinjection of protein into sensitized animals.

SYMPATHETIC GANGLIONEUROBLASTOMA E. BUSCH, *Acta path et microbiol Scandnav* **5** 289, 1928

A case with metastases is reported in a woman aged 30 years. This case is stated to be the sixth of its kind to be recorded. The five previously reported cases are reviewed briefly.

## Pathologic Chemistry and Physics

BILIARY ACIDS IN JAUNDICE I. KATAYAMA, *Arch Int Med* **42** 916, 1928

Quantitative studies were made of biliary acids in the blood and urine in various diseases of the biliary tract, and in other miscellaneous diseases. Biliary pigments in the blood were followed by the van den Bergh test, and the icterus index. The average biliary acids content of normal blood serum was 7 mg per hundred cubic centimeters, with no biliary acids in normal urine. Biliary acids appeared in the urine when the blood serum value reached 20 mg. Patients with cholecystitis, disease of the liver, catarrhal jaundice, obstructive jaundice, cardiac decompensation and duodenitis showed a marked increase of biliary acids in the blood serum, accompanied by excreted biliary acids in the urine.

HAMILTON R. FISHBACK

THE MANGANESE-COPPER-IRON COMPLEX AS A FACTOR IN HEMOCLOBIN BUILDING R. W. TITUS, H. W. CAVE and J. S. HUGHES, *J Biol Chem* **80** 565, 1928

Manganese added to a milk-iron diet seems to give almost, if not quite, as good results in the building of hemoglobin as does copper added in the same way. Manganese and copper added to a milk-iron diet appear to produce a quicker response from the standpoint of building of hemoglobin than does either copper or manganese when fed alone as a supplement. Experimental data presented seem to indicate the existence of a group of substances, rather than a single substance, which is active in the building of hemoglobin.

AUTHORS' SUMMARY

inoculation, in which a series of twenty-four specimens, negative by direct smear, was used, ten were negative by all methods. Fourteen others, 85.7 per cent, were positive by culture, while 72.8 per cent were positive by animal inoculation. Although one animal was positive with contaminated culture, three cultures grew from specimens that were negative on inoculation into guinea-pigs.

H J CORPER

THE FATE OF TUBERCLE BACILLI IN VARIOUS ORGANS H J CORPER and  
NAO UYEI, *Am Rev Tuberc* **18** 672, 1928

Guinea-pig inoculation is a far more delicate test for the presence of tubercle bacilli in tissues following intravenous injection of these bacilli into dogs and rabbits than are stained sections for bacilli or the development of tubercle or pathologic tissue changes in the organs of these animals. The morphologic changes in the bacilli occurring during their destruction in the organs of rabbits and dogs are difficult of determination when virulent bacilli are being used, because the number of bacilli are too few to be satisfactorily discernible by staining methods for this purpose. Comparatively large numbers of dead or avirulent bacilli must be given, so that they can be observed in stained smears with the microscope. Such observations as have been made make it seem likely that tubercle bacilli undergo the same changes in vivo as occur during cytomorphosis in vitro. As gaged from guinea-pig inoculation of the organs of rabbits and dogs at intervals after the intravenous injections of nonlethal amounts of virulent human tubercle bacilli, these bacilli are actively destroyed in the various organs of the rabbit and dog, although at a variable rate. In general, however, while viable tubercle bacilli were found early after injection into the circulation primarily only in the important organs of deposition, namely, the lung, liver, spleen, bone marrow and kidney, as these animals either succumb to the infection or survive, the bacilli would be found in the majority of the organs tested or would disappear following recovery from infection, leaving in many cases no appreciable histologic evidence of the presence of these bacilli except such as might occur in growing young animals, with impairment of the permanent parts of the body, such as the teeth and the bone. The animals given large amounts of bacilli usually pass through a symptomatic period of acute illness, which terminates either in recovery, with subsequent absence of disease, or a fatal outcome with generalized disease. In some cases, in which disease persisted or developed after a lapse of time, the lesions and presence of bacilli (as determined by guinea-pig inoculation) usually predominated in the organs previously reported from studies on organic tuberculosis as most susceptible to the disease, such as the lung of the rabbit and the liver and lung of the dog. The usual incidence of fatal outcome following intravenous infection was variable in the resistant animal given relatively large infecting doses, but the period lay between the first and the sixth month after infection, with the earlier months, following the first, being most consequential. After from six to nine months recovery was the rule.

H J CORPER

TUBERCULOSIS MORTALITY IN THE ORIGINAL DEATH-REGISTRATION STATES  
CORA E GRAY, *Am Rev Tuberc* **18** 687, 1928

From this general study certain facts are noted. 1 The peak of the death rate in adult life is not, for the area as a whole nor for most of the states, moving toward the older ages. During the twenty-five years under study it remained in the twentieth to the twenty-ninth year group. 2 Although there is a relation in the years from 1900 to 1924 between the death rate from tuberculosis and that from all other causes, there is none in the years from 1900 to 1904, and there is no relation between the decreases in the two death rates in the years under study. Presumably, the factors which now influence the death rate for tuberculosis are not those which affect the death rate from other causes. 3 The states with the highest death rates at the beginning of the period have made the greatest decreases, so that the range in the death rate for tuberculosis at the end of the period is much less than at the beginning.

H J CORPER

## Microbiology and Parasitology

THE CLINICAL SIGNIFICANCE OF THE LIFE CYCLE OF THE PARASITE IN INDUCED MALARIAS NICHOLAS KOPELOFF and CHARLES O FIERTZ, Am J M Sc **176** 664, 1928

A detailed microscopic study of the life cycle of a single strain of malaria inoculated intravenously into 300 patients with general paralysis reveals a total absence of gametocytes. The asexual cycle of this strain is identical with that of mosquito malaria. Such a strain is of practical value in the treatment for general paralysis in that (a) it eliminates the possibility of the transmission of malaria to other members of the community, and (b) it precludes the occurrence of malarial relapse following adequate administration of quinine.

PEARL ZEEK

EXPERIMENTAL SUBCUTANEOUS RHEUMATIC NODULES B I CLAWSON, Am J Path **4** 565, 1928

By injecting streptococci into the subcutaneous tissues of rabbits, lesions can be produced which are morphologically similar to the nodules found in the subcutaneous tissue in cases of acute rheumatic fever. Since these experimental nodules obviously occur as a result of injecting streptococci, the probable conclusion is suggested that acute rheumatic fever and the type of inflammation associated with it are of streptococcic origin.

AUTHORS SUMMARY

THE REGENERATION OF ACID-FASTNESS IN APPARENTLY DEGENERATED TUBERCLE BACILLI HENRY C SWEANY, Am Rev Tuberc **18** 630, 1928

Two unusual strains of tubercle bacilli were studied under unfavorable conditions. Degeneration forms were observed and described. In addition to the forms reverting directly to acid-fast bacilli, there are some that appear to have degenerated to a temporary nonacid-fast condition. These organisms are sometimes slowly growing coccoid or bacillary forms that are capable of reverting rather quickly to typical tubercle bacilli. Sometimes they may be rapid-growing, granular, bacillary or diphtheroid forms that revert to typical organisms after one or more animal passages. In the return to their characteristic form these organisms regenerate by a gradual transition that appears to be simultaneous with a corresponding change in the pathologic features. The organisms appear to become gradually acid-fast, beginning in the granule, which is also the last to lose it on regeneration. Cultures were grown from the end-products of these experiments which resembled the human tubercle bacillus. The pathologic change produced was at first exudative but gradually passed over into a more proliferative type with "epithelioid" and giant cells. It is believed that these facts will help to explain some obscure clinical and bacteriologic observations in tuberculosis.

H J CORPER

THE CULTIVATION OF THE TUBERCLE BACILLUS HENRY C SWEANY and MAX EVANOFF, Am Rev Tuberc **18** 661, 1928

The authors use 3 per cent sodium hydroxide for twenty minutes to destroy contaminants and concentrate the material. Whenever possible they inoculate directly without treatment because a caustic agent may be detrimental to a certain number of tubercle bacilli. Inhibiting substances have been practically abandoned, reliance being placed on a careful preparation of the material and a selective environment. Several culture mediums have been described, and two of them are recommended for use, one consists of veal egg medium, in which the veal is leached with sterile milk instead of water as in the Petroff method, and the other is like the first except that 10 per cent sterile cream is substituted for glycerin. More than 90 per cent of positive results were obtained consistently by these methods with less than 15 per cent of contamination. The cream medium is especially good for growing the bovine tubercle bacillus. In comparing these mediums with animal

Indians and others feed their dogs on raw wall-eyes and great northern pike, the dogs become an important reservoir of broad tapeworm and reinfest the fish in the lakes. Dogs are capable of harboring from five to nineteen broad tapeworms.

Fish in lakes near Indian reservations are most heavily infested. Three large Indian reservations are located on the shores and islands of Lake Nipigon with another reservation on the Nipigon river, which probably accounts for the heavy infestation in the Nipigon fish.

Indian agents and teachers should be instructed to teach the Indians the necessity of cooking fish even for dogs for the sake of dog, fish and man.

Lumbermen and their families in lumber camps should be inspected for tapeworm and treated if infested.

The importation of adult tapeworms by immigration should be prevented.

AUTHOR'S SUMMARY

MATT AND GLOSSY FORMS OF HEMOLYTIC STREPTOCOCCI E W TODD and R C LANCEFIELD, J Exper Med **48** 751 and 769, 1928

Hemolytic streptococci, when freshly isolated from pathogenic lesions, form characteristic matt colonies and contain the type-specific substance M. Two varieties of matt cultures, equally rich in type-specific substance, can be distinguished by the virulence of the organisms for mice: the matt virulent variety, the matt attenuated variety. The matt forms of hemolytic streptococci can be degraded to a third variety which forms glossy colonies and is always relatively avirulent. This is accomplished by prolonged cultivation on artificial mediums, by selection of colonies or by cultivation in homologous anti-M serum. In the process of degradation, the cocci lose the major part of their type-specific substance, but complete disappearance of type-specific substance rarely occurs. The glossy variant form, when fully degraded, is highly stable, but glossy cultures which have retained some type-specific substance can occasionally be reverted to the original matt form. Toxic filtrates from matt and glossy cultures are approximately equal in skin reactivity. No relationship appears to exist between virulence and toxigenicity.

The matt and the glossy forms of four strains of hemolytic streptococci were used to immunize rabbits. Precipitin tests showed that rabbit serums prepared against matt organisms, whether virulent or avirulent for mice, contained type-specific antibody, while serums prepared against completely degraded glossy organisms contained no type-specific antibody. Type-specific antibody was removed from the serums by absorption with homologous matt organisms but was unaffected by absorption with homologous glossy organisms. Passive protection experiments on mice showed that antimatt serums were protective and antiglossy serums non-protective against infection with homologous virulent organisms. Vaccination of mice with matt organisms rendered them immune to subsequent infection with homologous virulent cultures, but vaccination with glossy organisms established no active immunity.

AUTHORS' SUMMARY

EXPERIMENTAL TYPHOID FEVER IN THE GUINEA-PIG WILLIAM H HARRIS and OGILVIE M LARIMORE, J Exper Med **48** 885, 1928

During the activity of peritonitis produced in the guinea-pig by means of *Bacillus typhosus*, there is formed in the exudative material a filtrable toxic moiety which when inoculated into normal animals of this species produces certain of the clinical phenomena and a pathologic picture simulating that of human typhoid fever.

AUTHORS' SUMMARY

A STATISTICAL STUDY OF SCARLET FEVER AND DIPHTHERIA HILDA M WOODS, J Hyg **28** 147, 1928

The mortality from scarlet fever has declined relatively the most at the ages between 0 and 5 years, and there is a tendency for a greater proportion of the mortality to occur among older children and young adults.

THE DEVELOPMENTAL CYCLE OF THE TUBERCLE BACILLUS AS REVEALED BY SINGLE CELL STUDIES MORTON C KAHN and JOHN C TORREY, Am Rev Tuberc **18** 815, 1928

The results of studies of more than 200 preparations of single tubercle bacilli each in a separate microdroplet, under conditions which often ensured active growth and in such a manner as to maintain them in actively viable form for several days and often weeks, are recorded. Transplants were maintained on Long's synthetic medium with agar or gelatin. Branching forms, segmentation, globoid and coccoid forms are described. Nonacid-fast types were numerous.

H J CORPER

THE FILTERABILITY OF THE TUBERCLE BACILLUS WILLIAM P THOMPSON and MARTIN FROBISCHER, JR, Am Rev Tuberc **18** 823, 1928

Acid-fast bacilli may be found in the lymph nodes of 35 per cent of normal guinea-pigs. These results do not warrant the assumption of an invisible form of tubercle bacillus capable of passing through a filter candle, and capable of infecting and killing guinea-pigs.

H J CORPER

A POSSIBLE SOURCE OF SO-CALLED SPONTANEOUS TUBERCULOSIS IN GUINEA-PIGS HENRY SEWALL, Am Rev Tuberc **18** 829, 1928

In establishments which harbor tuberculous patients and in which the animal caretakers may be tuberculous, meticulous precautions should be exercised to be sure that guinea-pigs kept for experimental purposes are maintained in an uncontaminated environment, the food supply should have had no contact with the subjects of tuberculosis, nor, it may be assumed, should persons with tuberculosis be allowed to care for them. If children were studied instead of guinea-pigs it will be admitted that the conditions under suspicion would sufficiently explain the advent of alimentary and contact tuberculosis.

H J CORPER

THE RELATION OF PLASMODIUM FALCIPARUM TO THE HUMAN RED BLOOD CELL AS DETERMINED BY SECTIONS HERBERT L RATLIFF, Am J Trop Med **8** 559, 1928

Placental tissues from a person infected with *Plasmodium falciparum* were fixed in Bouin's fluid, dehydrated and embedded in paraffin. Sections 2 microns thick were cut and stained in Harris' hematoxylin. The parasites have been found invariably to be intracellular.

AUTHOR'S SUMMARY

UNDULANT FEVER IN CONNECTICUT T P MURDOCK and W E HALL, Ann Int Med **2** 545, 1928

Three cases of undulant fever were discovered by the writers in Meridan, Connecticut. The serum agglutinated *B abortus* to 1:300.

WALTER M SIMPSON

THE DOG A RESERVOIR OF THE BROAD TAPEWORM TEUNIS VERGEER, J A M A **92** 607, 1929

Broad tapeworm is common in the wall-eyes and great northern pikes of the large Canadian lakes. The fish in Lake Nipigon apparently are the most heavily infested. The adult worms have been brought over from Europe by infested Scandinavian, Finnish and Russian immigrants.

In some small lakes in lumbered forest regions, from 50 to 75 per cent of the wall-eyes and great northern pikes are infested.

The lumbering concerns employ Scandinavians and Finns almost exclusively, they cause the original infestation of fish in the small lakes, and as lumbering operations advance they move on.

Feeding autolyzed, boiled or autoclaved suspensions of the washed bacteria had little, if any, effect. Filtrates of twenty-four hour cultures produced a higher mortality rate than those from cultures which were incubated for longer periods of time.

In its remarkable heat stability this poison resembles the other toxic materials which have been described in the paratyphoid group, but its surprisingly long incubation period seems to separate this toxic substance definitely from that responsible for the violent gastro-intestinal symptoms occurring in man after eating foods containing these bacteria, and from any other toxic product of these bacteria that has yet been described.

Further investigation will be necessary before it can be determined whether this toxic principle is a product of the bacterial cells or a chemical poison formed by the action of the micro-organisms on the constituents of the medium.

AUTHORS' SUMMARY

EXPERIMENTS WITH GUINEA-PIG VACCINIA VIRUS J O W BLAND, Brit J Exper Path 9 283, 1928

Vaccinia virus from lesions of the skin of guinea-pigs fails to pass collodion membranes which allow the passage of serum globulins. Treatment of such membranes with serum increases their permeability to protein. The virus can be thrown down by high speed centrifugation for from two to two and one-half hours. The particles with which this virus is associated are possibly within the limits of microscopic visibility.

PEARL ZEEK

BACTERICIDAL POWER OF "WHOLE" BLOOD STUDIED BY CULTURE IN SLIDE-CELLS J M ALSTON, Brit J Exper Path 9 300, 1928

The slide-cell method of testing the bactericidal power of whole blood is described, and is found to be reliable. Diurnal variations are found in the bactericidal power of the blood of healthy persons and animals. Other transient changes are produced by a wide variety of substances.

PEARL ZEEK

THE EFFECT OF ULTRAVIOLET LIGHT ON THE VIABILITY OF THE VIRUS OF FOOT AND MOUTH DISEASE I A GALLOWAY and A EIDINOW, Brit J Exper Path 9 326, 1928

The virus of foot and mouth disease in filtrates is destroyed after five minutes' exposure to the radiations of the mercury vapour lamp in quartz flasks, which transmit radiations of wave lengths of from 5,720 to 2,300 Angstrom units, it is inactivated after thirty minutes' exposure to the rays of the mercury vapour lamp filtered through a sheet of vita-glass which allows the passage of rays of wave lengths of from 5,720 to 2,800 Angstrom units. The rays of wave lengths of from 5,720 to 2,300 Angstrom units have no lethal action on the virus of foot and mouth disease. When the virus is suspended in unfiltered lymph or serum, a protective action due to selective absorption by the suspending fluid is observed.

AUTHORS' SUMMARY

BEHAVIOR OF THE BACTERIOPHAGE IN THE PRESENCE OF NONSOLUBLE MICRO-ORGANISMS PAUL FABRY, Arch internat de med exper 4 413, 1928

The bacteriophage does not multiply in the presence of nonsoluble micro-organisms. In certain cases, however, if a susceptible species of organism is added to the combination of bacteriophage and apparently nonsoluble micro-organism, the bacteriophage multiplies in the same manner as when added to a culture of readily soluble organisms, thus indicating that there may be a beginning of lytic action though it is not apparent.

PEARL ZEEK

The mortality from diphtheria appears to be concentrated on children of the early school age and decreased at older ages

The decline in incidence and mortality from scarlet fever has been as great in towns with little isolation as in those in which the majority of patients are hospitalized

It cannot be shown that during the period studied isolation has had either a good or bad effect on the prevalence or mortality of scarlet fever

As far as the analysis goes and the method of correlation can show, there is no evidence pointing to the advantageous results of the isolation of patients with diphtheria in London

AUTHOR'S SUMMARY

A HEMOLYTIC SUBSTANCE IN PNEUMOCOCCUS CULTURE BROTH G M SICKLES and J M COFFEY, J Infect Dis 43 490, 1928

There is present in the culture broth of pneumococcus strains of different types and degrees of virulence a substance which has the property of lysing red blood cells This substance was produced when pneumococci were grown in several different mediums and appeared after from four to twelve hours' incubation depending on the medium and the strain The most potent substance was obtained when the pneumococcus strains were grown in beef-infusion broth plus 1 per cent dextrose, plus calcium carbonate with a small surface exposed to the air

The hemolytic substance is thermolabile and is destroyed by heating for thirty minutes at 55 C Its activity is diminished by standing at cold-room temperature and, in a shorter time, at 37 C The hemolytic substance may be absorbed from the culture broth by sheep red cells, horse stroma, guinea-pig leukocytes, animal charcoal and alumina Normal horse serum has an inhibitory effect on the hemolytic power of the substance while pneumococcus immune serum has a much more marked effect

AUTHORS' SUMMARY

STUDIES ON BOTULINUS TOXIN E WAGNER SOMMER and H SOMMER, J Infect Dis 43 496, 1928

On incubation of neutral botulinum toxin in salt solution at 37 C a decrease in potency of from 90 to 99 per cent occurred in twenty-four hours The deterioration was accelerated in alkaline mediums, but was greatly retarded at  $pH$  4.3 The addition of serum caused an immediate increase in toxicity, in several samples a further rise in the titer of the toxin was observed on incubation Witte's peptone showed the same influence as serum but in a less marked degree Dilution in a 20 per cent aminoid solution greatly stabilized the toxin The addition of lecithin slightly increased the initial titer of the toxin No effect was observed with sodium stearate and oleate Sodium ricinoleate caused rapid though not immediate inactivation of the poison

The results are discussed in the light of the protoxin and toxinase theories

AUTHORS' SUMMARY

A POISON PRODUCED BY BACTERIUM ENTERITIDIS AND BACTERIUM AERTRYCKE WHICH IS ACTIVE IN MICE WHEN GIVEN BY MOUTH SARA E BRANHAM, LUCILE ROBEY and LOIS A DAY, J Infect Dis 43 507, 1928

Seventeen strains of paratyphoid bacteria, isolated from foods or rodents, or from persons infected during food poisoning outbreaks, produced fatal infection in 100 per cent of mice to which they were fed These strains included seven of *Bacterium enteritidis*, nine of *B aertrycke* and one of *B schottmulleri*

When boiled broth cultures and Berkefeld N and W filtrates of broth cultures of these strains were fed similarly to mice, a mortality rate of approximately 40 per cent occurred

When whole unfiltered cultures in beef heart medium are boiled or autoclaved, and then fed to mice, the mortality rate is often from 40 to 100 per cent



BACTERIOLOGY AND SEROTHERAPY IN ACUTE APPENDICITIS M WEINBERG, A-R PREVOT, J DAVESNE and CLAUDIE RENARD, Ann de l'Inst Pasteur **42** 1167, 1928

The authors believe that appendicitis is always associated with bacterial invasion. Of the aerobes, *B. coli* was found in 87 per cent of the cases and the enterococcus in 30 per cent. The most common anaerobe was *B. perfringens*, which was found in 30 per cent of the cases. In 41 of 160 cases, *B. coli* and the enterococcus were found associated with or without other organisms. In 51 of 160 cases, *B. coli* and *B. perfringens* existed together in the same specimens. Experiments with rabbits indicated that the latter combination might be most important in appendicitis. An antigangrene serum in which the anti-oedematis traction was replaced with anticolon serum was used with good results.

M S MARSHALL

EXPERIMENTAL RESEARCH ON THE PATHOGENICITY OF CHOLERA P ZDRODOWSKI, Ann de l'Inst Pasteur **42** 1242, 1928

The author confirms and extends Sanarelli's work. An anaphylactoid reaction, called by the author The Phenomenon of Sanarelli, follows a state of hypersensitivity produced by a homologous or heterologous protein. Lesions in various organs and tissues, primarily in the epithelial and endothelial system, resulting from this reaction pave the way for the invasion by otherwise often harmless organisms. This opens the way for a new conception of intestinal diseases, explaining perhaps the pathogenicity in Asiatic cholera and cholera nostras, and some forms of appendicitis and ulcerous processes in the intestines.

M S MARSHALL

THE PATHOGENESIS OF RELAPSE IN EXPERIMENTAL RELAPSING FEVER A M BRUSSIN and G J ROGOWA, Centralbl f Bakteriologie **105** 39, 1928

After briefly reviewing the literature concerning the mechanism of relapse in recurrent fever, the authors describe experiments utilizing the "beladungs" phenomenon in the mouse. This consists in mixing the spirochetes with citrated blood from an immunized mouse, if the antibodies in the latter, called thrombocytobarrines, are specific, the spirochetes will become covered with blood platelets. The technical features and advantages of the procedure are described. By means of this method, the authors confirmed the earlier observations of Levaditi and Roche and of Manteufel that the antigenic properties of spirochetes of the first and second relapses of African relapsing fever are changed, in addition they confirmed the observation of Rosenthal with regard to the same effect with spirochetes from European relapsing fever. After the second relapse, the ability of the spirochetes to acquire new antigenic properties lessened in most instances, and usually the latter were identical with those of the second relapse. Clinical cure depends on the accumulation of antibodies against both the infecting strain and the relapse variants.

PAUL R CANNON

THE DEMONSTRATION OF VACCINE VIRUS IN THE BLOOD AFTER CUTANEOUS INOCULATION E GILDERMEISTER and GEORG HEUER, Centralbl f Bakteriologie **105** 86, 1928

The cutaneous injection of variola vaccine into rabbits was followed by its appearance in the blood within as short a time as two hours, it remained there for several days, as demonstrated by the method of Calmette and Guérin. The injection of a suspension of Pelikan ink (25 cc) had no influence, the authors thereby concluding that blockading the reticulo-endothelial system has no influence on the demonstration of the vaccine virus in the blood stream.

PAUL R CANNON

UNITY OF THE SPIROCHAETES OF THE DUTTON GROUP CHARLES NICOLLE and CHARLES ANDERSON, Arch de l'Inst Pasteur de Tunis **17** 321, 1928

Three strains of spirochetes of the so-called Dutton group, from various sources, are shown to be identical. In view of the fact that the spirochetes are so widely distributed geographically and that they may reside in various hosts, the results are of importance in infection and in vaccination

M S MARSHALL

NOTE ON MOROCCAN RECURRENT FEVER PIERRE HORNUS, Arch de l'Inst Pasteur de Tunis **17** 327, 1928

Recurrent fever, observed in certain parts in Morocco, has a predilection for Europeans during the fall. The disease develops around piggeries. The parasite which transmits it seems to be found in the soil around habitations and retains its virulence for a considerable time. The spirochete, the etiologic agent, may be inoculated into guinea-pigs, in which a series of attacks are produced analogous to those in man.

AUTHOR'S SUMMARY

FIXED VIRUS DOES NOT PASS INTO THE CENTRAL NERVOUS SYSTEM IN THE COURSE OF ANTIRABIC TREATMENT P. REMLINGER and J. BAILLY, Ann de l'Inst Pasteur **42** 729, 1928

The authors present experimental evidence in support of their title.

M S MARSHALL

STUDIES OF FOOT-AND-MOUTH DISEASE H. VALIEL and H. CARREL, Ann de l'Inst Pasteur **42** 841, 1928

There seem to be two races of the virus of foot-and-mouth disease, called O and A. Waldmann and Trautwein have added a third type (C). The only differentiation between the O and A types is based on immunity reactions, but these appear constant, the immunity from each being valueless against the other type. The O type is most common in France, England and Germany, but both types are found in various countries. Immunity following a first infection appears complete in both cases. Reinoculation under unknown conditions may bring about initial susceptibility instead of hyperimmunity.

AUTHORS' SUMMARY

TRANSPLACENTAL INFECTION WITH TUBERCULOUS ULTRAVIRUS AND TUBERCULOUS HEREDITY A. CALMETTE, J. VALTIS and M. LACOMME, Ann de l'Inst Pasteur **42** 1149, 1928

The authors consider the transplacental transmission of the normal form of the tubercle bacillus to be infrequent. It was demonstrated in only three of twenty-six infants of tuberculous mothers. Transplacental transmission of the filtrable ultravirus is much more common. It appears particularly intense after from three to six months' gestation in women with developing tuberculosis, especially the pulmonary or meningitic type. Usually these are fatal to the child in the first weeks after birth. Then, since the death rate in the first two months of life of infants born of tuberculous mothers does not appear to exceed 20 per cent, and the number of children of tuberculous mothers born with the ultravirus is greater (perhaps 80 per cent), it may be concluded that perhaps nearly 60 per cent of the new-born carriers of the ultravirus support this infection without immediate harm. There seems to be some immunity. The matter is being studied. Thus far the distinction between transplacental transmission of the tubercle bacillus and of the ultravirus does not in any way indicate a change from the procedure of separation from the mother or the use of B. C. G.

M S MARSHALL

increase in the tubercles. None of the types of light rays used (carbon arc, mercury vapor, and alpine sun lamps) called forth a material difference in the process. One animal, which received repeated injections of eosin and was kept in weak diffuse light, showed a general reaction against tuberculosis, consisting of fibrous encapsulation of most necrotic foci. The author concluded that neither long nor short wave light rays influence the course of tuberculosis in guinea-pigs.

B R LOVETT

PRIMARY TUBERCULOSIS OF THE MIDDLE EAR IN INFANTS M ZARFL, Virchows Arch f path Anat **266** 274, 1927

The author investigated thoroughly four instances of primary tuberculous infection of the middle ear, in which the regional lymph glands were involved, and which presented the picture of a primary complex. Clinically, swelling of the auricular glands appeared first, followed by discharge from the ear, facial paralysis and swelling of the mastoid, with a positive tuberculin reaction in three cases. Pathologic investigation revealed indubitable tuberculous changes with the presence of tubercle bacilli in the structures of the middle ear, and failed to reveal a primary complex in any other part of the body. The infection apparently began in the mucous membrane, and spread to all nearby structures—the labyrinth, middle ear, facial canal, bony walls, etc. Infection probably entered through the eustachian tube. This could take place either during birth, through aspiration of infected amniotic fluid, or afterward from a person with open tuberculosis. In two of these cases the mother, and in one the father, suffered from tuberculosis, in the other, no source of infection could be found.

B R LOVETT

VARIOLA-VACCINIA HANS DEMME, Ztschr f Immunitätsforsch u exper Therap **55** 191, 1928

The problem of neurotropism of the variola-vaccinia virus was investigated. Inoculations were made into the cornea, skin, testicle, sciatic nerve and subdural space of rabbits. Encephalitis was absent in all rabbits inoculated in peripheral organs. Pleocytosis of the spinal fluid following inoculation was interpreted as evidence of the participation of the central nervous system in the defensive reaction of the organism. There was no indication that the virus wanders by way of the nerves, on the contrary, the fact that the clinical course was the same after inoculation into the sciatic nerve, with and without previous surgical interruption, and the occurrence of cases of general vaccinia after inoculation of this nerve and the cornea point to the carriage of the virus by the blood. The encephalitis occurring after intracerebral inoculation was a nonspecific inflammatory reaction restricted to the meninges and vascular sheaths (mesenchymatous reaction) without participation of the ectodermal nervous substance. As these results differ from those after inoculation of herpes virus, variola-vaccinia does not belong to the neurotropic ectodermatoses. Its close relationship to herpes is denied. The vaccinia infection is interpreted as a general infection. It may activate a virus already present in the body or prepare the field for its activity. This interpretation applies also to human postvaccinal encephalitis.

WILLIAM C HUEPER

THE DESTINY OF TYPHOID BACILLUS INTRODUCED PER OS INTO DOGS T. OUCHI, Scient Rep Gov Inst Inf Dis **6** 1, 1927

The coprophagic habits of dogs when hungry may be an important factor in the extrahuman persistence of the typhoid bacillus. Human excrement when ingested by dogs passes directly into the bowel without stopping long in the stomach and hence does not receive the bactericidal action of the gastric juice.

E P JORDAN

A NEW CAUSE OF MOUSE SEPTICEMIA (*CORYNEBACTERIUM MURISEPTICUM* N SP) GERTRUD FREIIN VON HOLZHAUSEN, Centralbl f Bakteriöl **105** 94, 1928

The author describes an organism isolated from the brain of a rabid dog which regularly causes a fatal septicemia in mice. The organism is a gram-positive rod to which the name *Corynebacterium murisepticum* n sp is given. The bacterium is peculiar in that only the endothelial cells of the blood vessels appear to phagocytose it, the usual reticulo-endothelial cells remaining free.

PAUL R CANNON

RARE GRAM-NEGATIVE ANAEROBIC BACILLI AS UNUSUAL CAUSES OF ACUTE INFECTIONS OF THE MIDDLE EAR ERICH WIRTH, Centralbl f Bakteriöl **105** 201, 1928

Wirth describes anaerobic gram-negative bacilli isolated from two unusually severe infections of the middle ear. The organisms are pleomorphic, gas-forming and pathogenic for mice, guinea-pigs and rabbits. He thinks that they may be identical with *B. funduliformis*.

PAUL R CANNON

THE CHANGES IN THE MIGRATION OF ASCARIS LARVAE IN THE BODY OF THE HOST G G SMIRNOW, Centralbl f Bakteriöl **105** 426, 1928

The migration of *Ascaris* larvae in mice and guinea-pigs experimentally infected with embryonated eggs causes definite changes particularly in the wall of the cecum, in the liver and the lungs. The intensity and character of these pathologic changes depend on the degree of the invasion. The reaction in the compact tissues of the liver is less marked than in the porous tissues of the lungs. In response to the presence of the larvae there is an infiltration of eosinophils, polymorphonuclear leukocytes and a proliferation of macrophages, tending to encapsulate the larvae, with later fibrous changes and even calcification. The larvae in the liver enter through the portal vein and may enter the bile passages secondarily, but not primarily. The reactions in the lungs are predominantly mesenchymal. There is practically no invasion of other organs. Previous stimulation of the macrophages by vital staining appears to render the protection against the larvae more marked.

PAUL R CANNON

THE TRANSMISSION OF INFECTIOUS RAT ANEMIA MARTIN MAYER, Klin Wchnschr **7** 2390, 1928

The rat louse, *Haematopinus spinulosus*, has been found to be a vector for infectious rat anemia.

E F HIRSCH

EXPERIMENTAL SYPHILIS OF THE CENTRAL NERVOUS SYSTEM I L KRITSCHIEWSKI and E S HERONIMUS, Klin Wchnschr **7** 2472, 1928

The tropism of *Spirochaeta pallida* for the central nervous system is almost absolute, and various strains may not be classified into neurotropic and dermatropic.

E F HIRSCH

THE EFFECT OF LIGHT RAYS ON EXPERIMENTAL TUBERCULOSIS IN GUINEA-PIGS H LOWENSTADT, Virchows Arch f path Anat **266** 99, 1927

Guinea-pigs were inoculated subcutaneously with tubercle bacilli, and the effect of light rays on their general condition and on the histologic picture was observed. The controls presented a variable picture with regard to necrosis and encapsulation. In the spleen, demarcation of the tubercles took place, and in the lymph nodes

THE ABSENCE OF HETEROPHILIC ANTIGEN IN CERTAIN FOODS I DAVIDSOHN,  
J Infect Dis **44** 44, 1929

Twenty-six rabbits were given injections of watery suspensions of cabbage, lettuce, carrots, potatoes, wheat, corn and oats, with their alcoholic extracts and of a mixture of these alcoholic extracts and pig serum to determine whether the foregoing substances contain heterophilic antigen. The immunization was not followed by an increase of the antishoop hemolysin. Cabbage, lettuce, carrots, potatoes, wheat, corn and oats do not contain heterophilic antigen of the Forssman type.

AUTHOR'S SUMMARY

ACID AGGLUTINATION OPTIMUM IN THE BRUCELLA GROUP E E ECKER and  
M A SIMON, J Infect Dis **44** 62, 1929

Four strains of *Brucella melitensis* and *abortus* of different origins were studied. Their acid agglutination optimums were found to be identical, a fact which is believed to be of interest in the consideration of their close relationship, if not their identity.

AUTHORS' SUMMARY

HEMOLYSIN AND HEMAGGLUTININ FOR SHEEP CORPUSCLES IN HUMAN SERUMS  
OF ALL ISOAGGLUTINATIVE GROUPS. ETHEL B PERRY and G BERNICE  
RHODES, J Infect Dis **44** 65, 1929

Hemolysin for sheep corpuscles is present in human serums of all iso-agglutinative groups, though not in all serums of any group, while the heterophilic hemagglutinin is present in nearly all human serums. The dilutions of serum in which hemagglutinin is best demonstrated, 1:1 to 1:3, are often inhibitory for hemolysis. Of 143 serums, 80 were hemolytic for sheep corpuscles in dilutions ranging chiefly from 1:12 to 1:192 with the limiting titer most frequently 1:48. The titers of the lytic A serums were not lower than those of other groups. The hemolysin is independent of the iso-agglutinin and is absorbable by the kidney or liver of the guinea-pig.

AUTHORS' SUMMARY

HEMOLYSIN FOR SHEEP CORPUSCLES IN PRECIPITIN SERUMS FROM RABBITS  
LUDVIG HEKTOEN and ETHEL B PERRY, J Infect Dis **44** 68, 1929

Precipitin serums from rabbits immunized with egg white, cow's milk, blood (beef, chicken, dog), sheep serum, swine euglobulin, human pseudoglobulin, and hemoglobins, fibrinogens and thyroglobulins of many different species contain hemolysin for sheep corpuscles. Tests repeated after absorption of the serums with the homologous antigen and with sheep corpuscles indicate that the hemolysin is independent of the precipitin. The possibility of traces of lipid (also of other substances) must be considered since in the separation of serum proteins the lipoids are known to be precipitated with the globulins.

AUTHORS' SUMMARY

THE RELATIONSHIP BETWEEN THE HAEMOLYTIC COMPLEMENT AND THE OPSONIC  
POWER OF GUINEA-PIG SERUM JOHN GORDON, HUGH ROBINSON WHITE-  
HEAD and ARTHUR WORMALL, J Path & Bact **32** 57, 1929

Destruction of the hemolytic complement activity of normal guinea-pig serum by small amounts of ammonia does not reduce to any significant extent the opsonic power of the serum for *Staphylococcus aureus*. Incubation of the normal serum at 37 C for two hours with this organism, in amounts sufficient to remove the opsonic and hemolytic complement activities, does not remove the fourth component of complement. The conclusion is drawn from this evidence that one component of complement at least, the fourth component, is not essential for the opsonic action of the normal serum.

AUTHORS' SUMMARY

## Immunology

THE TESTICULAR ALLERGIC RESPONSE IN GUINEA PIGS FOR THE DIAGNOSIS OF TUBERCULOUS FLUIDS J J WIENER, JOHN E BLAIR and HENRY L JAFFE, *Am Rev Tuberc* **19** 55, 1929

In making a diagnosis, an attempt was made to apply Long's testicular tuberculin reaction to the body fluids suspected of coming from tuberculous foci. The test consists of the injection of from 0.1 to 0.3 cc. of the suspected fluid into the testis of a tuberculous guinea-pig, autopsy on the animal after from five to seven days, and the histologic examination of the testis for a characteristic degeneration. The diagnostic value of the test is impaired by the fact that about 35 per cent of nontuberculous fluids (particularly fluids from cases of malignant tumor) gave a reaction which was histologically indistinguishable from that given by tuberculous fluid. Data obtained show that this is a toxic effect, which apparently cannot be eliminated by reduction of the amount of fluid injected. However, if from 0.1 to 0.2 cc. of the fluid from a suspected tuberculous focus, with the exception of spinal fluids, does not produce the aforementioned reaction, on inoculation into the testis of a tuberculous guinea-pig, the possibility of tuberculosis of that focus may be definitely ruled out.

H J CORPER

THE MODE OF ACTION OF FORMALDEHYDE ON COMPLEMENT FIXATION SYSTEMS C E REYNER, *J Immunol* **16** 1, 1929

The action of formaldehyde in intensifying the fixation of complement is due to its action on the antigen.

SURFACE TENSION OF BLOOD SERUM IN SYPHILIS ELIZABETH M YAGLL, *J Immunol* **16** 17, 1929

Determinations of surface tension are of no value as a means of differentiating between syphilitic and normal serum. The so-called "syphilitic antibody," or reagin, is evidently not highly surface active or at least not more highly active than other substances found in normal and in syphilitic serum.

AUTHOR'S SUMMARY

SERUM DILUTION AND ANTIGEN DENSITY AND THE NON-SPECIFIC PRECIPITATIONS OF FOWL SERUM S J SCHILLING and G S SCHILLING, *J Immunol* **16** 61, 1929

Increasing antigen density markedly decreases the nonspecific precipitation reaction in fowl serums. The most abundant precipitates are frequently found in dilutions of phenolized saline solution. This menstruum also regularly caused the precipitations in the highest dilutions of fowl serum. Grades *Salmonella pullorum* antigens of increasing densities showed a gradual fall in the highest dilution of fowl serum at which such respective antigens yielded precipitate. Evidence is adduced that a lipoidal element is responsible for the nonspecific precipitation reaction.

AUTHORS' SUMMARY

VENOMS OF NORTH AMERICAN SNAKES AND THEIR RELATIONSHIP THOMAS S GITHEUS and LEWIS W BUTZ, *J Immunol* **16** 71, 1929

The venoms of six species of North American rattlesnakes, which were studied, contain identical or almost identical toxic principles. The toxic principles of the copperhead and moccasin are identical or almost so, but differ to some extent from those of the rattlesnakes. The venom of *Crotalus terrificus* the dog-faced rattlesnake of Central and South America, and the venom of *Bothrops atrox*, the fer de lance, contain principles differing entirely from those of the Nearctic rattlesnakes as regards their antigenic properties. Rattlesnake venoms contain, in addition to their acutely toxic principles, other components which have the power to bind antibodies but which are not acutely toxic to pigeons.

AUTHORS' SUMMARY

embryos begins at six and one-half months. The group antigens of differentiated embryos are held in the fixed organ cells (liver, kidney, spleen, brain) and in the erythrocytes. Group antibodies of human embryos were at times not demonstrable even in the last months of intra-uterine life.

AUTHOR'S SUMMARY

PECULIAR SKIN REACTION CAUSED BY HUMAN BLOOD R. ROSSLE, Munchen med Wchnschr **75** 1789, 1928

For a number of years Rossle observed at necropsies that the contact of cadaver blood with the skin of the flexor service of his forearm caused red spots to appear in from twenty to thirty minutes. These spots disappear in from one half to three quarters of an hour. The degree of the reaction varies with the amount of blood, the contact of a large quantity of blood leaves a red ring surrounding a white blanched center. This phenomenon may sometimes be produced even with blood from living and closely related persons. Its cause is not only mechanical but also chemical substances quickly produced during the escape of the blood irritate the skin.

EDWIN F. HIRSCH

INFECTION AND IMMUNITY OF THE SKIN IN ANTHRAX T. BAUTZ and C. AMIRASLANOW, Ztschr f Immunitatsforsch u exper Therap **56** 1, 1928

The cutaneous method of vaccination by Besredka is by far superior to the subcutaneous one. There is no elective susceptibility of the skin to anthrax as asserted by Besredka.

W. C. HUEPER

TUBERCULIN AND FIBROBLASTS ALBERT FISCHER, Ztschr f Immunitatsforsch u exper Therap **56** 24, 1928

Tissue cells of tuberculous persons react in vitro after addition of tuberculin with no morphologic changes, but with an increased tendency to grow at certain concentrations of the tuberculin. Strains of fibroblasts cultured over a longer period in a medium containing small amounts of tuberculin acquire a definite resistance against tuberculin in large doses. Strains treated with tuberculin react on the addition of tuberculin or bouillon in certain concentrations with increased proliferation.

W. C. HUEPER

THE INHIBITION OF BACTERIAL GROWTH IN HUMAN SERUM WOLFF, Ztschr f Immunitatsforsch u exper Therap **56** 279, 1928

The inhibition of the growth of streptococci for the first five hours, if grown in blood serum exposed to the air for some time, depends on the strong alkaline reaction ( $pH$  8) of the serum, to which the cocci have to adapt themselves. The growth of *Bacillus coli*, *Bacillus typhosus* and *Bacillus anthracis* is not inhibited under the same condition. Rabbit serum does not possess this inhibitory quality. The process is regarded as important for the healing of wounds.

W. C. HUEPER

THE ACTIVE IMMUNIZATION OF CHILDREN AGAINST SCARLET FEVER S. KORSCHUN and H. SPIRINA, Ztschr f Immunitatsforsch u exper Therap **56** 288, 1928

For the immunization of children against scarlet fever the authors recommend three series of injections of a vaccine containing, in 1 cc, 1 billion of streptococci killed by formaldehyde and 2,000 skin units of toxin, followed each time by an injection of toxin. The toxin had to be free from protein substances. The frequency of scarlet fever dropped after the introduction of this method from 10 to 167 times and fatal cases disappeared almost completely. The Dick reaction became negative in 89.8 per cent of cases. The injection of too high amounts of vaccine may result in the production of a typical scarlet fever syndrome. Increase in temperature and local reaction are usually the only symptoms following injection.

AGGLUTINATION OF RECURRENT FEVER SPIROCHAETES HELENE SPARROW,  
UGO LUMBROSO and MARIO LAPIDARI, Arch de l'Inst Pasteur de Tunis  
17 279, 1928

No difficulty was encountered in demonstrating specific agglutination of various strains of spirochetes classified by Dr Nicolle and his co-workers in the basis of pathogenicity and of immunity. The serum used was secured from animals which had recovered from an infection, sometimes diluted as much as one hundred times with rabbit serum. The spirochete suspension consisted of citrated blood containing a large number of fresh organisms. Incubation of a mixture of the two for half an hour or an hour was followed by examination under the ultramicroscope. Prolonged incubation may result in the lysis of spirochetes, but correct incubation results in a roset-like arrangement often around blood cells or platelets without necessarily loss of motility.

M S MARSHALL

EOSINOPHILIA OF THE BLOOD AFTER INJECTION OF FOREIGN PROTEINS AND  
IN HEMOCLASTIC SHOCK V SPOUJITCH, J de physiol et de path gen  
26 655, 1928

Spoujitch injected foreign proteins into several kinds of animals and found that there was considerable difference in the eosinophilic response of the various species. During different phases of anaphylactic shock, produced by subcutaneous or intraperitoneal injection, the eosinophils and neutrophils responded as one group. After shock in man and in most animals there is no eosinophilia, though in guinea-pigs eosinophilia is pronounced.

THE BACTERICIDAL PROPERTY OF CEREBROSPINAL FLUID AS WELL AS INFLAM-  
MATORY AND NONINFLAMMATORY EFFUSIONS OF THE CHEST AND ABDOMEN  
P VON GARA, Klin Wchnschr 7 2386, 1928

Many of the spinal fluids examined had no bactericidal properties for gram-positive micro-organisms (anthrax, staphylococci). The spinal fluids from two idiots, however, were markedly bactericidal. A relation between this bactericidal property and the Wassermann or Sachs-Georgi reactions could not be established. There were no differences when the material was obtained from patients with or without inflammatory diseases of the meninges. Inflammatory pleural and peritoneal effusions with high specific gravity were markedly bactericidal. This property was fully active even after eight days. Transudates from the chest and abdomen and the noninflammatory fluid of an ovarian cyst were not bactericidal.

EDWIN F HIRSCH

SKIN REACTION WITH THE APPLICATION OF DIFFERENT RHUS SPECIES H  
BIBERSTEIN, Klin Wchnschr 8 99, 1929

Sensitivity, sensitization and desensitization experiments were tried with six different varieties of *Rhus*. The individual *Rhus* varieties of the same season stimulate with varying frequency, and the irritability of the same variety in different years is not the same. The number of persons reacting increased with the increase in the number of *Rhus* varieties. With sensitization and desensitization the varieties and seasons vary (as in I). Sensitization develops with varying rapidity and in a varying percentage of cases. Certain varieties during a given year sensitize 100 per cent. Primarily susceptible persons could not be sensitized toward other *Rhus* varieties more than those naturally insusceptible. The favoring influence of trauma was confirmed. Sensitization sometimes occurred in waves. Desensitization was accomplished as a rule even in those primarily hypersensitive.

AUTHOR'S SUMMARY

THE GROUP SPECIFIC DIFFERENTIATION OF HUMAN TISSUES O M SEMZOWA  
and A A TERECHOWA, Klin Wchnschr 8 206, 1929

Human embryos are undifferentiated up to six months so far as antigenic group properties are concerned. The antigenic group differentiation of human



epidermal origin of these tumors. He states that the lack of pigment in the skin of these tumors is an expression of rapid growth and failure of maturation and differentiation of the cells. His belief is based on the demonstration of malignant changes beginning in the basal cell layer. These tumors are very malignant and treatment is of little avail. More than one half of his cases were cases of tumors of the lower extremities in patients past middle age.

N ENZER

AN EXPERIMENTAL STUDY OF THE ETIOLOGY OF CHICKEN SARCOMA I (ROUS)  
W E GYE and J HOWARD MUELLER, J Exper Med **49** 195, 1929

Acriflavine in itself is a very feeble antiseptic toward the virus of the filtrable fowl sarcoma. Proof of this statement has been obtained by allowing acriflavine to act on filtrates in which cysteine has been dissolved to prevent loss of infectivity by oxidation. Under such circumstances, a very active filtrate cannot be sterilized (in twenty-four hours) with any possible concentration of acriflavine. Feebly active extracts are rendered inert in twenty-four hours by dilution of acriflavine of 1:10,000. In these experiments the acriflavine is neutralized before being added to tumor extracts, otherwise, precipitates are formed which nullify the experiment. When the infectivity of a Rous tumor extract is destroyed by the action of acriflavine in the presence of fresh horse serum, the result is governed by the viricidal action of the serum, acriflavine acting in a merely supplementary way.

AUTHORS' SUMMARY

HYPERNEPHROMA WITH SUPRARENAL APLASIA. CLAIRE DEBARGE, J de physiol et de path gen **26** 639 and 668, 1928

Debargé discusses the case of a previously healthy man, aged 90, who died apparently of bronchopneumonia. Autopsy disclosed, in addition to the pneumonic observations, complete absence of the right suprarenal gland, there was none on the left at the superior pole, but a small mass was found in the retroperitoneal tissue near the tail of the pancreas. Serial sections of this mass revealed nothing which could be identified as suprarenal tissue but there was considerable tuberculous caseation. The right kidney contained a tumor mass which almost doubled its normal size. It consisted microscopically of fibrous tissue, necrotic material, and typical suprarenal cortical cells. Chromaffin cells could not be identified by staining. The tumor cells showed characteristic malignant changes. The author concludes in his second paper that prolonged life is possible with an infinitesimal number of suprarenal cortical cells, and that a strictly cortical malignant hypernephroma can reproduce exactly the function of normal suprarenal cortical cells.

A CASE OF SARCOMA DEVELOPING AFTER RADIUM TREATMENT OF EPITHELIOMA IN THE TEMPORAL REGION. AAGL WAGNER, Acta radiol **9** 370, 1928

A description is given of an epithelioma which during treatment with radium is transformed to a sarcoma. Next, the possible causes of the development of the sarcoma are discussed. These are assumed to be as follows: (1) the origin of the tumor as a carcinosarcoma of which only the carcinoma component was destroyed by treatment, (2) the irritative effect of the carcinoma cells on the connective tissue, (3) the influence of roentgen rays on the connective tissue, and (4) direct metaplasia of the epithelial cells.

AUTHOR'S SUMMARY

THE NATURE OF THE ENTITY TRANSMITTING CHICKEN SARCOMA AS EVIDENCED BY EXPERIMENTS ON DESICCATED SARCOMA TISSUE. W NAKAHARA, Jap J Exper Med **7** 101, 1928

The power of the dry tissue of the Rous sarcoma to transmit sarcoma in chickens is seriously impaired by grinding in mortar. The improbability that a chemical substance can be damaged greatly by grinding is emphasized, and it is concluded that the transmission of chicken sarcoma depends on a foreign body, probably the sarcoma cell itself.

tion The immunity produced lasts in general more than a year Vaccination does not protect against the common complication of scarlet fever Vaccination is contraindicated in nephritis, uncompensated heart lesion and acute infectious diseases The toxin used for the Dick reaction must be freed from proteins to avoid a pseudoreaction A positive Dick reaction indicates an increased susceptibility to scarlet fever

W C HUEPER

THE INFLUENCE OF CHOLESTEROL ON EXPERIMENTAL ANAPHYLAXIS L SURANYI and L JARNO, *Ztschr f Immunitatsforsch u exper Therap* **56** 303, 1928

Reinjection with cholesterinized serum does not prevent anaphylaxis Animals in which the blood cholesterol is increased by cholesterol feeding before reinjection succumb without exception to anaphylactic shock Blood with an increased cholesterol content contains a decreased amount of complement An interrelation exists between the decrease of complement in anaphylaxis and in cholesteremia and the anaphylactic disposition in cholesteremia

W C HUEPER

THE NATURE OF IMMUNITY IN RELAPSING FEVER I KRITSCHESKI and S SCHAPIRO, *Ztschr f Immunitatsforsch u exper Therap* **56** 308, 1928

The destruction of the spirochetes and the recovery with the maximal amount of immunity bodies is observed in animals with a well preserved reticulo-endothelial system Rats in which the spleen is removed die from relapsing fever with a complete absence of spirochetolysins The introduction of antibodies into rats splenectomized or with a blocked reticulo-endothelial system or both at the time of or after infection, acts as a substitute for the lacking function of the reticulo-endothelial system The mechanism of the defensive function of this system in relapsing fever is represented, therefore, by the secretion of immunity bodies and not by the phagocytic action of the cells

W C HUEPER

THE CONNECTION BETWEEN BLOOD PLATELETS AND SPINDLE-SHAPED CELLS, ACCORDING TO IMMUNITY METHODS F T GRUNBAUM, *Virchows Arch f path Anat* **267** 126, 1928

In the agglutination of trypanosomes and spirochetes with blood platelets, the other cells of the blood played no part The platelets of mammals, however, could be replaced in this reaction by the spindle-shaped cells of birds, but not by those of frogs The platelets of mammals and the spindle cells of birds, therefore, have similar powers They also have an independent origin, and are not related to the other formed elements of the peripheral blood Concerning their origin, it can only be said that it is closely connected with the bone marrow, but to which cells of the marrow their development is due, remains a question The spindle cells of amphibia do not correspond to the third blood elements of mammals and birds

B R LOVETT

IMMUNOLOGICAL STUDIES OF THE CONSTITUENTS OF *BACILLUS DYSENTERIAE* (SHIGA) K MATSUMOTO and T SEKI, *Jap J Exper Med* **7** 1, 1928

The nucleoprotein of *Bacillus dysenteriae* is antigenic in vivo as well as in vitro, whereas the residual substance which reacts specifically with antibacterial serum has no power to induce the formation of antibodies in vivo

## Tumors

MELANOTIC TUMORS A HORWITZ, *Ann Surg* **87** 917, 1928

This article contains a valuable review of the theories advanced concerning the nature of melanotic tumors, chiefly of the skin The subject of the origin and fate of melanin is also discussed Horwitz is inclined to accept the theory of the

OCCUPATIONAL AMYOTROPHIC LATERAL SCLEROSIS M GUNTHER and P HOCH,  
Deutsche Ztschr f d ges gerichtl Med **12** 68, 1928

This disease is said to result from strains, severe trauma of the central nervous system, toxemias of different sorts, exposure to cold and other exciting causes in persons predisposed by heredity. The lesions of the cord were formerly regarded as altogether made up of retrogressive changes, but considerable evidence of inflammation has been found by recent studies. The suggestion has been made that the disease may sometimes have an infectious or toxic origin and extend to the nervous system by lymph channels. With the advent of such explanations for its etiology, the relation of amyotrophic lateral sclerosis to occupational disorders and hazards has assumed importance. After reviewing all the circumstances it was decided that two soldiers of the World War were entitled to compensation for having this disease, that in one of them it followed getting wet and severely chilled, and in the other, acute rheumatism due to exposure. A third patient with amyotrophic lateral sclerosis was denied compensation because there were no grounds for supposing it was related to a primary tuberculosis of the eyes.

E R LE COUNT

ALCOHOLISM IN THE TYROL P VOGLER, Ztschr f d ges Neurol u Psychiat  
**111** 661, 1927

From many of the institutes of psychiatry of the universities of Austria and Germany there have appeared during the past few years reports of the way the World War affected the numbers of patients with chronic alcoholism, delirium tremens, alcoholic psychosis and other late effects of the use of alcoholic beverages. Similar studies have also been made in Switzerland and Denmark. To these, Vogler adds a statement of what has been noted in that part of western Austria which lies directly east of Switzerland and north of Italy, a portion of Europe not previously embraced. He found a remarkable correspondence between the condition met with there at Innsbruck and those noted in other parts of Europe. He mentions fourteen writers who have made similar studies. Apparently a large part of middle Europe has now been gone over in these investigations.

In all these countries there was a marked subsidence of these manifestations of chronic alcohol poisoning. This began with, and continued throughout, the war. During the reconstruction period there was a gradual return to prewar conditions, and since then the consumption of alcohol has steadily increased so that now it considerably surpasses anything heretofore known, judging by the numbers treated for its effects in these institutes. The review by Vogler comprises a report of 1,857 cases in which the patients were cared for during twenty-three years, ten before and eight since the war. The fall and rise in the number of patients treated, in percentage of the total number cared for and the numbers of men and of women treated all matched one another closely.

E R LE COUNT

### Technical

THE HINTON GLYCEROL-CHOLESTEROL PRECIPITATION REACTION IN SYPHILIS  
C MORTON SMITH, Arch Dermat & Syph **19** 439, 1929

As a rule, the Hinton reaction gives a smaller number of so-called "doubtful" readings. It is claimed also that the reaction becomes positive earlier than does the Wassermann and at least as soon as the Kahn reaction. The incidence of false positive reactions is reduced. There are few conditions, thus far recognized, that give false positive reactions. Another point in favor of the Hinton test is that it is possible to work with anticomplementary and somewhat hemolyzed blood. This fact is often of great value to the clinician. It requires far less training to be able to read results of the Hinton test than those of either the Kahn or the Wassermann test. It is applicable to spinal fluid as well as to blood serum. It is apparently more nearly a specific test for syphilis than the others.

AUTHOR'S SUMMARY

CYTOCHROME IN TUMOR TISSUES H YAOI, H TAMIYA and W NAKAHARA, Jap J Exper Med 7 109, 1928

Cytochrome, the intracellular respiratory pigment discovered by Keilin, was found in large amounts in Fujinawa rat sarcoma and in smaller amounts in Fleener-Jobling rat carcinoma and Bashford mouse carcinoma, Rous chicken sarcoma contained little or no pigment

### Medicolegal Pathology

PUNCH DRUNK H S MARTLAND, J A M A 91 1103, 1928

This sequence of repeated blows on the head occurs in prize fighters and is marked by staggering, mental confusion, dragging of one foot, a tilted head and parkinsonism. It may be the beginning of mental disease requiring subsequent confinement. It is said to result from small hemorrhages in the cerebrum, which are really contusions, and from the alterations to which they lead. Martland found such hemorrhages in 9 of 309 brains of persons with injured heads, none, however, with broken cranial bones. Fractures of these bones are said to interfere with the production of these effects of concussion, presumably by release of pressure which is necessary for tearing by fluids forced by the blows into places too small to contain them. The lesions are chiefly in the basal ganglions.

E R LE COUNT

THALLIUM POISONING J H T DAVIES and M C ANDREWS, Brit M J 2 1139, 1927

Two sisters, aged 11 and 8 years, respectively, were given thallium acetate, 85 mg per kilogram of body weight to one and 875 mg to the other. One became severely poisoned with pains in the knees on the twelfth day, four days later the lower extremities became hot, swollen and tender, while on the eighteenth day there was fluid in the knee joints and the patient had convulsions. She was discharged after ten days of treatment in a hospital, but the knees and legs were still tender on the thirty-fifth day. The scalp of each girl became completely hairless for a time.

EXPERIMENTAL STAB WOUNDS K FUJIWARA, Deutsche Ztschr f d ges gerichtl Med 12 65, 1928

When the features of stab wounds are hidden by drying and clotted blood, they may be fully restored even as long as forty-eight hours after they are made, by washing them with warm water. The size and other peculiarities of stab wounds of the skin are considerably modified by the degree of tension or relaxation of the skin when the wound is made. Stab wounds of the skin and of viscera differ somewhat although made with the same weapon. In parenchymatous organs they do not gap as much, and the end of the wound corresponding to the back of weapons with only one cutting edge are wider than the knife back is thick, in the skin they may be narrower. That the wounds have been made with a weapon with only one cutting edge is usually easily determined by this greater width of the wound at one end. But this may be difficult to decide when the blade is thin. The shape of the wound at the wide end generally matches that of the knife back and may be square or have several angles. When the back of the blade is flat, one of the two corners of the wide end of the wound is usually indented more than the other in the surface of the skin. Tension of the wound end to end often helps to explain the shape of the weapon. When the wound gaps, its length is less than the width of the blade used, but straightening it so as to lay the edges together before measurements are made may yield a dimension greater than that of the width of the knife or sword employed. These are some of the more important conclusions Fujiwara made by a study of wounds of the shaven skin of anesthetized dogs. He used altogether sixteen different weapons—pocket knives, daggers, stilettos, household and butcher knives, knives used in several industries and army weapons.

E R LE COUNT

# Society Transactions

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## NEW YORK PATHOLOGICAL SOCIETY

*Regular Meeting, Feb 13, 1929*

HARRISON S. MARTLAND, M.D., *Presiding*

### VIRULENT ANTHRAX BACILLUS FROM A CASE OF MALIGNANT PUSTULE IN MAN ADELE E. SHEPLAR and MARJORIE B. PATTERSON

On Dec 31, 1928, P. W., a man, appeared at the outpatient department of the New York Post-Graduate Hospital with a lesion on the right side of the neck of five days' duration. He was sent to the laboratory for bacteriologic examination. The lesion presented a very dark crater-like center, approximately 15 mm in diameter, surrounded by confluent vesicles containing a pink-colored thin fluid, the total area approximating 50 mm in diameter. Microscopic examination of the fluid obtained from the vesicles revealed large numbers of spherical organisms evidently staphylococci and a few large rods. Plate cultures showed large numbers of colonies of staphylococci and a smaller number of typical Medusa head colonies of the anthrax bacillus.

On intraperitoneal inoculation into a mouse, a saline suspension of the colonies killed the animal within fifteen hours, and on subcutaneous inoculation into a guinea-pig produced death in thirty-six hours. A small fragment of the spleen of the guinea-pig was placed in a subcutaneous pocket of a rabbit and this animal died after five days with extensive subcutaneous edema about the point of inoculation. A secondary infection was present, however, and necropsy disclosed a complicating old pericarditis, possibly due to previous use of the animal for bleeding by heart puncture. A second rabbit was inoculated by placing a loopful of a twenty-four hour agar slant culture of the third cultural generation of this strain into a subcutaneous pocket. This animal died after sixty hours. Subcutaneous hemorrhagic edema was slight and limited to the region of the inoculation, an area approximately 40 by 50 mm. The anthrax bacilli were found distributed through all the organs and present in the heart blood.

The patient was employed as a chauffeur by a furniture dealer and part of his time was used in furniture repair and upholstery work. It is probable that he had come into contact with animal hair. He said that the lesion had begun as a small pimple at the side of the neck some five days before. After appropriate serum treatment, the patient made a good recovery.

The observation is of interest because the lesion here corresponds to the classic malignant pustule and contains anthrax bacilli of full virulence similar to the Pasteur virus strain capable of killing rabbits. The nature of the animal hair concerned in the present instance is unknown.

### RESORCINOL TESTS IN RELATION TO DISEASES WITHOUT CONCOMITANT TUBERCULOSIS ADELAIDE B. BAYLIS

A report of 163 tests on 156 patients with various diseases, without recognized concomitant tuberculosis, tested by resorcinol flocculation, reveals the fact that certain diseases other than tuberculosis are capable of giving false reactions. It is, therefore, concluded that when these diseases exist without apparent concomitant tuberculosis, diagnostic observations should be confirmed by further laboratory and clinical examinations. A comparison of the Vernes and Baylis tests shows a close correlation between the two methods, and while they are useful in differential diagnosis, their chief value lies in their ability to measure the degree of activity in recognized tuberculosis.

AN IMPROVED TECHNIQUE FOR THE COMPARISON OF ANTISEPTICS BY YEAST FERMENTATION SARA E BRANHAM, *J Infect Dis* **44** 142, 1929

A simple device for quantitatively collecting the carbon dioxide produced by fermenting yeasts has been made. By this means, the principles of the method of comparing antiseptics by fermentation of yeast have been confirmed and shown to have a general application and the whole procedure has been put on a more dependable basis. This technic not only affords a simple and effective means of comparing the action of many types of antiseptics, but also offers an opportunity for the study of the phases of the process under observation. The simplicity of this method, as compared with the elaborate and laborious procedures employed in many laboratories, commends it for general use.

AUTHOR'S SUMMARY

ON PHOTOGRAPHING GROSS PATHOLOGICAL SPECIMENS W G MACCALLUM, *Bull Johns Hopkins Hosp* **44** 207, 1929

Specimens fixed by Kaiserling's method are photographed under water in a tank covered with plate glass. Details must be studied in the original.

A RADIOPAQUE BISMUTH SUSPENSION FOR ANATOMICAL, HISTOLOGICAL AND PATHOLOGICAL RESEARCH EBEN C HILL, *Bull Johns Hopkins Hosp* **44** 248, 1929

A method using bismuth oxychloride suspended in a solution of gum acacia has been found to be most satisfactory for postmortem roentgen study of the vascular systems. For most purposes a suspension of 20 per cent bismuth oxychloride in 11 per cent solution of acacia gives excellent delineation, but for specific tissues the percentages of both the bismuth and the acacia must be varied to secure optimal results. The acacia serves as an agent to aggregate the finely divided particles of bismuth, and by employing cloth filters of various meshes, unit masses of any desired size may be obtained. Tissue that has undergone an injection of this radiopaque suspension may be studied microscopically either as cleared specimens or in stained histologic sections, in both, the bismuth-filled area is clearly delimited from the surrounding tissues.

AUTHOR'S SUMMARY

THE SEDIMENTATION RATE OF ERYTHROCYTES H B NEWHAM and P H MARTIN, *Quart J Med* **22** 145, 1928

The present study was conducted in twenty-five patients suffering from sprue, kala-azar, malaria, secondary anemia, trypanosomiasis, cirrhosis, dysentery and amebic hepatitis. Liver function was determined by the levulose test. No change in liver function, however, was found which would parallel the changes in the rates of sedimentation. Differences in specific gravity of the erythrocytes apparently had no bearing on the phenomenon. The same is true of the viscosity of the plasma and of the size of the erythrocytes. One positive fact appeared, namely, that most of the rapidly sedimenting bloods showed auto-agglutination of the erythrocytes.

N ENZER

HEMATOXYLIN AS A REAGENT FOR IRON M MUHLMANN, *Virchows Arch f path Anat* **266** 697, 1928

Interested in the small quantities of iron in the central nervous system that do not give the ordinary reactions for this metal, the author investigated the possibilities of hematoxylin as an iron reagent. He concluded that staining with hematoxylin depends on an alkaline reaction and the presence of iron, usually suboxides. Two sorts of iron-containing substances were found, one in myelin sheaths which resisted the action of acids but disappeared after treatment with lipid solvents, and the other in the pigment of the substantia nigra and in the capillary endothelium, resistant to both reagents. He suggested phagocytized red cells as the source of the iron in the latter.

B R LOVETT

biochemistry of the prostatovesicular secretions, during which the most interesting phenomenon of glycolysis, or sugar or carbohydrate utilization by spermatozoa in the semen, was demonstrated, and it was then determined that spermatozoa in vitro, which after six hours had become sluggishly motile, could be markedly activated by the addition of 5 per cent dextrose solution. By a play of the imagination, one can readily see how, in an individual with sluggishly motile spermatozoa as a factor in incapacity for procreation, such spermatozoa might be revived in vivo. These studies, then, are a continuation of the study of glycolysis made some time ago. As Dr Killian has explained, the three important factors influencing the motility of spermatozoa are viscosity, osmotic pressure and reaction. The viscosity or plasticity—there being a fine distinction between the two terms—may be an important factor, and the motility of the spermatozoa may be restored to the maximum by the addition of equal volumes of 4.5 per cent dextrose, buffered with phosphates to  $p_H$  7.6. The reaction is probably least important because between  $p_H$  5 and  $p_H$  8.3 the motility remains unchanged and, during the study of glycolysis, it was observed that the reaction of the semen was  $p_H$  7.6 during the first six hours, despite the fact that there was an increase in lactic acid above 100 per cent of the control, there evidently being an efficient and effective buffer mechanism in the semen itself. These studies offer a fertile field for future investigation. A practical application has been made in only one instance. A couple, married eight years and anxious to have children, came to see Dr Killian. He advised them of the proper solutions to use and the proper strengths to employ, and the wife became pregnant.

J A KILLIAN. Dr Ravid raised the question of the influence of temperature on motility. From our own observations, we can definitely say that variations between 15 and 40 C have no demonstrable effect on the motility of spermatozoa. All these experiments were carried out between 20 and 25 C, so that we can exclude temperature as a factor influencing the motility. The only experiment which varied from that was one consisting in the addition of gelatin and the increase of viscosity by lowering the temperature.

THE HALOGEN BALANCE IN BROMIDE THERAPY OF EPILEPSY. J A KILLIAN, J NOTKIN, T GARCIA and L HALPERN

In this country, the use of bromides as antispasmodics has been discredited owing to the appearance of ominous symptoms and complications following their indiscriminate administration.

In order to secure the maximum antispasmodic effect and to obviate complications, the administration of bromides should be guided by a knowledge of their fate in the human organism and their influence on the components of normal body fluids.

In the study of the effect of ingested bromides in the treatment for epilepsy on the female service of the Manhattan State Hospital, we have determined the distribution of the halides between the blood plasma and the erythrocytes.

After the continuous administration of halides, the total halides are increased above the normal with a replacement of a portion of the chlorides by bromides. This does not influence the distribution of chloride between the blood cells and the plasma, and the bromide is distributed between blood cells and plasma in a manner similar to that of the chlorides.

Bromide is excreted in the urine with chloride in the same proportion in which these halides are found in blood. The bromine ion apparently does not diffuse into spinal fluid as readily as the chlorine ion. The blood plasma of epileptic persons on bromide therapy shows an opalescence which is not associated with any change in the lipins of the blood or the serum proteins of the blood.

DISCUSSION

J NOTKIN. Attention is called to the work of von Wiss, Frey, Ulrich and Bernoulli, particularly the latter, who has done considerable experimental work

## DISCUSSION

WARD J MACNEAL I should like to emphasize a point which Miss Baylis made at the end, in order that it may be clearly understood, because certain recent visitors to our laboratory appear not to have appreciated this point which Miss Baylis has attempted to emphasize in all the publications on this subject. Tuberculosis is not diagnosed satisfactorily by this test, we make the diagnosis of infection with the tubercle bacillus by entirely different means. This test, moreover, makes no pretense to measure the extent of the lesion in the body, however, it does appear to indicate the degree of activity of the process. Any one who is familiar with the pathology of tuberculosis will realize that we need this sort of a test. We already possess many means of diagnosing the presence of the tubercle bacillus in the body with a fair degree of accuracy and of measuring the amount of tissue involved. This resorcinol test does not purpose to do those things, it is used to indicate the state of activity of the tuberculous process.

FACTORS INFLUENCING MOTILITY OF SPERMATOZOA J A KILLIAN, J F MCCARTHY, C T STEPITA and M B JOHNSTON

Observations have been made on the influence of variations in viscosity, osmotic pressure and H-ion concentration on the motility of spermatozoa in semen.

Increasing viscosity of semen by the addition of gelatin solution was followed by a proportionate decrease in motility. Nonmotile spermatozoa in viscid specimens could be rendered motile by the addition of equal volumes of 0.5 molar dextrose.

A depression of the motility of spermatozoa followed the addition of aqueous solutions of nonelectrolytes to the semen. Molar solutions destroyed motility entirely. Five-tenths molar solutions depressed the motility to about one half the control. Urea, however, was a notable exception to this general rule.

Aqueous solutions of two ion salts depressed motility to a greater extent than nonelectrolytes, aqueous solutions of three ion salts diminished the motility below that observed for two ion salts.

Variations in H-ion concentration, between  $pH$  5 and  $pH$  8.3 did not influence the motility of spermatozoa, but increasing the H-ion concentration or decreasing it beyond these limits was followed by a depression of the motility.

## DISCUSSION

JACOB M RAVID I wonder whether one can draw any analogy from the motility of *B. coli*—*B. typhosus* groups or of any other motile bacteria to that of the spermatozoa. We know very well what an important factor temperature plays in the motility of micro-organisms. I should therefore like to ask the authors what their experience was in regard to this point and also whether they paid special attention to the temperature in all their experiments.

C T STEPITA This study of the factors influencing the motility of the spermatozoa of the semen, credit for which is in great part due to Dr Killian, was stimulated by a study by Drs McCarthy, Ritter and Klemperer, made at the laboratories of the New York Post-Graduate Hospital, relative to the anatomy and the histology of the verumontanum and the ejaculatory ducts. At this time it was demonstrated that catheterization of the ejaculatory ducts was feasible. By means of such catheterization the seminal vesicle, a hitherto obscure organ, is brought into the searching spotlight of orderly scientific scrutiny, and by this means not only the physical conformation but the unmixed bacteriology of the vesicles, as well as the viability of the spermatozoa in their natural habitat, may be determined. One has also the means of observing the reaction of the seminal vesicular secretions uncontaminated by the prostatic secretions and, finally, in the presence of sluggishly motile or dead spermatozoa it may be possible by direct treatment to remove the conditions inimical to their viability.

The present study was not concerned so much with the highly technical work of catheterization. We were more interested in the actual study of the specimens of semen. Dr Killian made a study a number of years ago of the



process At an early stage in the stroma, there were accumulations of pale cells which were larger than the tubular cells and had small dark nuclei, the glomeruli within such areas may show no lesion or early deposit of hyaline material within the tuft The large pale cells stained intensely with fat stains In frozen sections, the fat was double refractile The glomerular epithelium contained much less fat The lipoidal cells were in the interstitial tissue In the older areas, these cells were replaced by fibroblastic proliferation and lymphocytes The tufts of the glomeruli showed gradual filling up with hyaline material, which did not take the amyloid stain The tubular epithelium showed an uneven distribution of the finer and coarser fat globules with fat stain, mostly in the high epithelial cells of the convoluted tubuli of the first order and ascending portion of Henle's loop In the lumen of the tubuli casts were seen and many stained intensely with fat stain

Sections of the liver, suprarenal gland and retroperitoneal lymph node showed also accumulations of lipoidal cells, which were similar to those in the kidneys In the liver, the lipoidal cells showed transition to hyalinization and necrosis

From the pathologic observations it was obvious that we were dealing with a general constitutional condition The striking feature was the accumulation of lipoidal cells in many organs, this suggested a general lipoidosis of the endothelial cells with marked disease of the kidneys

The clinical picture corresponded to the pathologic observations in the interpretation of the glomerular changes which were secondary to the fatty and hyaline changes not unlike amyloidosis In many other respects, too, the condition showed some similarity to general amyloidosis

In this case we seemed to deal with a general lipoidosis, which had produced grave secondary anatomic changes in the kidneys, which then became responsible for the characteristic clinical picture There was morphologic as well as clinical evidence that the essentially tubular kidney disease of long duration terminated with advanced glomerular injury, causing renal insufficiency and uremia

#### DISCUSSION

HARRISON S MARTLAND I suppose there is no doubt from the clinical history of this case and the gross and microscopic studies that it is a typical nephrosis, such as has been described by Epstein The great controversy, however, is how many kidneys should one take away from the parenchymatous group and place in this category

#### ACUTE NEPHRITIS IN RATS AFTER INTRAVENOUS INJECTIONS OF COLLOIDAL LEAD LOUISE H MEEKER

The kidneys of albino rats show striking parenchymatous changes after lead poisoning

Our observations are based on forty-four rats treated with colloidal lead The lead solution was given intravenously for the most part In a few instances, subcutaneous and intraperitoneal injections were given The lead was prepared under the direction of Dr Sheplar The method was that of Woodward The actual amount of lead in each colloidal preparation was determined under the direction of Dr Killian Dr Killian also later analyzed the kidneys of the rats and found lead present

The duration of the lead treatment in the animals was as follows

1 for 55 days	1 for 36 days	5 for 19 days	1 for 12 days
2 for 54 days	1 for 30 days	1 for 18 days	1 for 9 days
1 for 52 days	3 for 25 days	1 for 17 days	2 for 8 days
1 for 47 days	2 for 21 days	5 for 14 days	1 for 7 days
4 for 44 days			

The number of injections varied from two to ten, the number of days between the injections varied from three to ten, seven days being the usual interval Ordinarily, the rats were killed two and three days after the last injection of lead In five instances, the last injection was seven, sixteen, eighteen, nineteen and twenty-nine days before death Four of the rats died from lead poisoning

with bromide in animals and men, and who finally evolved the conception of the "relative bromide content," which consists in a substitution of only a certain amount of sodium chloride by sodium bromide, and is expressed in a percentage rate. According to Bernoulli, the relative bromide content should not be higher than 20 in order to avoid the complications of bromide intoxication. In my experience, I have found that the relative bromide content may be much higher and the signs of complication are not always due to bromide intoxication but to lack of sodium chloride in the organism. I believe that what really matters is the necessary physiologic minimum of sodium chloride in the organism, which apparently varies from one person to the other, and from one race to the other. The Wuth's calorimetric method of bromide estimation in the blood is discussed, and here again I found very much higher figures. I shall show a comparative study of phenobarbital and bromide therapy of a large number of epileptic patients treated at the Manhattan State Hospital since July, 1926.

J A KILLIAN The undesirable effects of bromide therapy might be attributed to one of two conditions, either an accumulation of the bromide ion in the body tissues or fluid, or a loss of chloride. When it comes to the question of following these cases from the clinical standpoint, from the results shown on the chart it is evident that analysis of the urine is adequate because it is shown that the bromide is excreted in the urine in the same proportion in which it is in the blood. Consequently, from the urinalysis one can ascertain the relative concentrations of bromide and chloride in the blood.

#### THE SO-CALLED "LIPOID NEPHROSIS" NICOLAS M ALTER

Is "lipoid nephrosis" a disease entity with a pathologic process of the kidney that is responsible for the characteristic clinical picture? This is the obtruding question to any one familiar with this disease.

Clinical, but particularly pathologic data are still lacking and are much needed to attempt to answer this and many other questions that turn up during the study of this condition.

A white boy, aged 8 years, was admitted to Post-Graduate Medical School and Hospital on Aug 10, 1928, with edema of the forehead and legs and "urinary disease"—albuminuria and casts. On admission, the patient showed edema of the face and ankles. The blood pressure and temperature were normal. The chemical analysis of the blood showed urea nitrogen, 12.8, cholesterol, 0.357, albumin, 1.75, and globulin, 1.58. The blood count revealed red blood cells, 4,192,000, white blood cells, 15,200, and polymorphonuclears, 72 per cent. The present illness consisted in an aggravation of symptoms for the last three to four weeks, since a cold, but was practically continuous for from two to three years.

He had frequent colds and sore throat, whooping cough and infection of the ear in 1928. On Aug 22, 1928, the patient became acutely ill, with a temperature of 101 F, and convulsions. He died with symptoms of uremia on August 24. On August 22, the blood pressure was 108 systolic and 68 diastolic, the blood urea nitrogen was 25.8. On August 23 the blood pressure was 124 systolic and 100 diastolic, the blood urea nitrogen, 53.7. Autopsy was performed on Aug 24, 1928.

The body weight was about 30 Kg. General edema was present. The heart weight was 145 Gm. The thickness of the left ventricle was 7 mm. The weight of both kidneys was 375 Gm. Cross-section showed a uniformly thick cortex (13 mm) of a grayish, translucent, edematous appearance. There was a yellow somewhat opaque streaking. The papillae were dark. The renal pelvis was narrow. The liver weighed 765 Gm. The capsule was smooth. On cross-section, the parenchyma was pale brown throughout. Scattered uniformly small specks of yellow areas were seen. The suprarenal glands together weighed 8 Gm. The layers were thin and pale. The retroperitoneal lymph nodes measured from 2 to 3 cm in diameter, they were soft. The lungs were edematous.

Microscopic sections of the kidneys showed a striking picture. The streaks in the gross specimen corresponded to various stages of a progressive pathologic

As a rule, the glomeruli in the affected areas of the kidneys show no change. In some instances, however, the glomeruli show marked congestion and numbers of polymorphonuclear leukocytes and occasionally albuminous exudate in Bowman's space. In other words, the glomerular changes are always acute and transient. It is to this acute glomerular inflammation that we consider the hemoglobin and iron in these bodies is chiefly due. Lead does not unite with hemoglobin.

There are no changes in the collecting tubules, in the interstitial tissue or in the blood vessels. Forty control rats showed no kidney lesions as described for the rats treated with lead.



Fig 2—Rat 25 The experiment lasted twenty-five days with four intravenous injections. The total amount of lead injected was 38 mg. High power, hematoxylin and eosin. Rat 32 The experiment lasted fifty-five days with six intravenous injections. The total amount of lead injected was 111 mg. Eosin-staining bodies in pale nuclei with chromatin at the periphery are present. The black bodies in the lumen of the tubule show eosin-staining bodies in the center. High power, hematoxylin and eosin. Rat 23 The experiment lasted twenty-one days, with four intravenous injections. The total amount of lead injected was 35 mg. Black bodies are present in the lumen of the tubule. The larger body shows lamellation and crenations. The glomerulus (left) and blood vessel (above) show no pathologic changes. High power, hematoxylin and eosin.

The total amount of lead given to any one rat varied from 3 to 176 mg. The rat receiving 176 mg. was treated fifty-five days, and the largest amount of lead given at any one time was 26 mg., or twice the lethal dose.

The changes in the kidney were most evident in the second portion of the convoluted tubules (fig 1, *a* and *b*). The epithelial cells were swollen and the cell boundaries lost very early, with cell debris filling the lumina. The nuclei became swollen and pale with fragments of chromatin forming clumps. Ovoid bodies staining pink with eosin appeared near the nucleoli or by transformation of the nucleoli (fig 2, 32). As these bodies enlarged, the chromatin granules collected on their surface and the nuclear membrane slowly disappeared. The pink-staining bodies were extruded into the lumen of the tubule and became larger and darker. The outline of these now dark bodies usually showed serrations and lamellation, as many as eight or ten concentric lamellae being counted in many

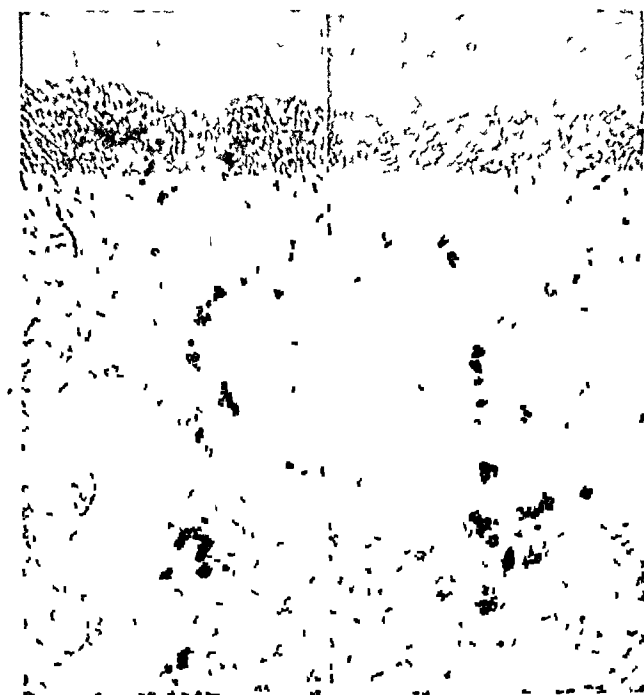


Fig 1—The black bodies are in the convoluted tubules *a*, after exposure to hydrogen sulphide in an acid solution, *b*, unstained. Frozen sections, low power.

instances (fig 2, 23). Tubules showing the early intranucleolar forms of these bodies occasionally showed mitotic figures in adjacent cells (fig 2, 25). Where these dark bodies were most numerous the tubule epithelium was entirely disintegrated. The bodies stain black when exposed to hydrogen sulphide in a weakly acid solution, indicating a lead content. They also stain blue by Perl's test for iron.

Bell has emphasized the affinity between lead and lecithin. It is suggested that lead may have united with the lecithin or a similar lipid in the tubule epithelium to form these bodies. To follow the complicated reaction between them would require *in vivo* studies similar to those of Leathes, MacLean and White, together with much further animal experimentation. Budding forms and minute droplets are seen and are similar in reaction to the larger bodies. These droplets also suggest myelin forms of lipins. The bodies are the only elements in the sections that give a positive lead reaction by microchemical tests.

*Regular Meeting, March 14, 1929*

HARRISON S MARTLAND, *President, in the Chair*

MULTIPLE FIBROMATOUS POLYPI OF THE INTESTINE, ASSOCIATED WITH CHRONIC TUBERCULOSIS OF THE ILEUM AND CECUM DAVID PERLA

An instance was reported of multiple fibromatous polypi of the intestinal tract in a middle aged man suffering from chronic hyperplastic tuberculosis of the intestinal tract. The polypi were most prominent in the rectum, where they produced partial obstruction because of the large size of the fibromatous masses. A correlation between the chronic tuberculosis of the intestine and the development of these tumors was suggested. To the author's knowledge, this is the second instance on record of multiple fibromatous polypi of the intestinal tract.

DISCUSSION

NICHOLAS ALTER It is known that tubercle bacilli have a stimulating effect on the surrounding tissue. They produce a specific granulation tissue, but whether it can produce a stimulation to other tissues of a neoplastic nature has not been sufficiently emphasized, although it has been mentioned time and again that there may be some relation between tuberculosis and malignant disease. Adler, in his monographs published sometime ago, showed a close relation between tuberculosis of the lung and carcinoma. In my experience, I often found malignant disease associated with tuberculosis. I remember a case of carcinoma of the esophagus associated with tuberculosis and another of testicular teratoma associated with tuberculosis, there are many other cases. I recall the old theory of Ehrlich that he propounded in connection with his carcinosarcoma in cancer produced in mice. Ehrlich brought forward the explanation that the whole course depends on the nutrition of the tissue and that the various tissues depend on various food supplies. This explanation would somewhat explain why in one case tuberculosis produces a specific granulation tissue and in another, a proliferation of a neoplastic nature. I am thoroughly convinced that tuberculosis and cancer have a close connection.

HARRISON S MARTLAND I do not know whether I missed some of Dr Perla's remarks, but did I understand him to say that multiple fibrous polypi in the colon constituted an unusual or rare lesion?

DAVID PERLA Yes

HARRISON S MARTLAND In the case presented, did you interpret the polypi as existing before the tuberculous ulcers?

DAVID PERLA That question would be difficult to answer. I intimated that there might be some relationship between the long-standing chronic hyperplastic tuberculosis of the intestinal tract and the development of these multiple fibromatous polypi. It is well known that in association with chronic irritations of the intestinal tract with strictures, and with hyperplastic tuberculosis, polypi are frequently seen, in strictures produced by neoplastic changes, one sees filiform elongated polypi around the stricture, so there is no doubt that chronic irritation can stimulate the overgrowth of mucous membrane sufficiently to produce these tumor formations. On that basis, I suggested the possibility that the long-standing infection might also have stimulated the peculiar fibromatous processes.

MYASTHENIA GRAVIS WITH MULTIPLE THYMIC GRANULOMAS NICHOLAS M ALTER

The pathologic process of this rare disease is still the subject of a great deal of controversy. Every case that can bring additional information should be recorded. The extensive postmortem observations warrant this report.

A white woman, aged 31, married, was admitted to the New York Post-Graduate Hospital on Sept 26, 1928 with the chief complaints of ptosis, internal strabismus, dysphagia, dysphonia, dysmimesis, general weakness and loss of weight. The illness began about six months before admission with ptosis of both lids.

In summarizing, it may be said colloidal lead produces a destruction of tubule epithelium of the kidney somewhat similar to the action of other metals, such as mercury. The portion of tubule affected is that concerned in elimination. Recovery may occur after one, two or three insults, but finally the regenerative capacity is destroyed and no further recovery is seen. Individual rats vary greatly in their susceptibility to colloidal lead. Lead may be recovered from the kidneys showing the lesions described.

#### DISCUSSION

JAMES EWING Did you find any colloidal particles of lead in the endothelial cells, such as are found in cases in man?

LOUISE H. MEEKER There were no particles of lead in the endothelial cells of the kidney. The spleen and liver have not been carefully studied by me as yet. My purpose at this time has been to show a definite reaction to lead in the kidney since this has been frequently disputed. We believe that we have a reaction comparable to that of other heavy metals.

HARRISON S. MARTLAND It is hardly fair to compare the experience I have had with a very stable and apparently nontoxic form of colloidal lead with that of those using colloids approaching the Blair Bell type. Our lead was phagocytosed to an enormous extent by the histiocytes of the reticulo-endothelial system and very little ever reached the malignant growth. In time, however, it was toxic and produced terrific uncontrollable anemias. In human beings and in animals it was very toxic to the kidneys and produced intense nephritis.

#### ARRANGEMENT OF THE SMALLER ARTERIAL VESSELS IN THE SPLEEN WARD J. MACNEAL and JACOB M. RAVID

Human spleens from necropsies and from surgical operations were fixed in the distended state by arterial perfusion (MacNeal, W. J., Otani, Sadao, and Patterson, M. B. The Finer Vascular Channels of the Spleen, *Am J Path* 3: 111 [March] 1927). Serial sections at a thickness of 5 microns have then been prepared. For study of the course of the arteries and veins, drawings of every tenth section at a magnification of 20 diameters were made, transferred to wax plates 1 mm thick, and these plates were put together for reconstruction of the vessels and follicles in relation to them.

For study of the finer arterial vessels pertaining to an individual lobule, each serial section was drawn at a magnification of 200 diameters, and reconstruction was carried on in the same manner.

The models are not yet finished. The reconstruction, however, has progressed to such a point that the architecture of the splenic lobule and the interrelationships of the lobules and blood vessels have been disclosed. As a rule, the arterial supply of each lobule is terminal, but occasionally one may recognize a slender communicating arterial twig coming from an adjacent trabecular artery and joining on to the eccentric arteriole of the lobule. From the eccentric artery there are given off the follicular capillaries, which form an anastomosing meshwork of thin-walled closed capillaries within the follicle and terminate by opening into the intercellular pulp spaces of the marginal zone of the lobule. These vessels are minute, often collapsed in part, and are extremely difficult to trace in serial sections. Larger branches of the order of fine arterioles take origin from branches of the eccentric artery and extend into the marginal zone, where they are surrounded by the ellipsoid sheaths of Schweigger-Seidel. They give off recurrent or centripetal capillaries which curve toward the follicle and terminate by opening out into the intercellular pulp spaces of the marginal zone. Other small branches arising from the same vessels continue in a centrifugal direction as the capillaries of pulp cords, to terminate in the intercellular spaces of the pulp cord at a distance from the follicle.

leukemias incorrectly diagnosed. A certain type of an anemia, however, in which an unusually large number of nucleated red cells is found, does occur in infants, these red cells sometimes outnumber the leukocytes and constitute an outstanding feature because of which this condition should be classed as a distinct type of anemia of unknown etiology.

Occasionally during the past seven or eight years, an infant born at full term with anemia and showing such an unusually large number of erythroblasts in the blood, has been admitted to the Babies' Wards at the Post-Graduate Hospital, the cases of three such infants were described. The first was that of a boy, aged 9 months, who was a mongolian idiot. The blood picture showed 125 nucleated red cells to 100 leukocytes. The second case was that of a boy, aged 5½ months, with malnutrition, who showed 92 nucleated red cells to 100 leukocytes. The third was that of a boy, aged 6 months, who had malnutrition and disease of the middle ear and showed 110 erythroblasts to 100 leukocytes.

From the study of these cases, the most conspicuous feature seen is the unusually great abundance of immature red cells, far greater than in the usual form of secondary anemia, in which erythroblasts do occur, therefore, it would seem that a more suitable name for this condition would be erythroblastic anemia, or erythroblastemia of infants, instead of pseudoleukemia infantum or von Jaksch's disease.

#### DISCUSSION

HARRISON S. MARTLAND. I suppose that all these cases would have been diagnosed von Jaksch's anemia.

B. R. WHITCHER. That was the diagnosis made formerly.

HARRISON S. MARTLAND. Although I am opposed to giving new names to diseases of the blood unless their etiology is definitely determined, the designation suggested, "erythroblastemia of infants," is perhaps more descriptive than von Jaksch's anemia.

JAMES EWING. Were any of the nucleated red cells easily confused with lymphocytes?

B. R. WHITCHER. No. On the whole, especially in the first case, the nucleated red cells showed little polychromatophilia. In some the cytoplasm showed a slight lavender color, and in others a slight slate color, but in most of them it showed the same salmon-pink color that the nonnucleated red cells did. In the other cases, the nucleated cells in some instances showed a slight slate color, and some of the cells showed rather ragged edges, but they could readily be distinguished from the lymphocytes.

JAMES EWING. You said that the diagnosis of leukemia was thought of.

B. R. WHITCHER. That diagnosis was thought of, but after making the second count I decided there was no leukemia, and that the condition was von Jaksch's disease.

HARRISON S. MARTLAND. I do not believe that in these cases there is any doubt about the identity of the nucleated red cells. There is usually no difficulty in accurately identifying cells in blood smears. Identification is not so easy, however, in sections of bone marrow in which it is often impossible, even by special stains, to state whether certain cells are of erythroblastic, myeloblastic or even lymphoblastic origin. For this reason, I have long advocated the study of smears of bone marrow in preference to sections for accurate interpretation.

JAMES EWING. I have an idea that some of the so-called low-grade leukemias of infants are of this type, in which the nucleated cells with little or no hemoglobin are mistaken for lymphocytes.

B. F. YOULAND. In the medical service of Flower Hospital, an infant was born who died about five days after delivery. At autopsy, the skin presented a distinctive pale, indefinite, yellow color suggestive of pigmentation and apparently resembling that described by Dr. Whitcher. When the body was opened, the internal tissues and organs presented a somewhat similar discoloration. The

Two months before death, she began to have difficulty with speech. For the past ten days, she could not swallow. There was a gradually increasing weakness of the muscles of the back, neck and jaw. On physical examination, the patient was well nourished and had marked ptosis of both eyes, more marked on the left than on the right. She had internal strabismus. There was bilateral paralysis of the face. The patient could not laugh. Speech, swallowing and breathing were greatly impaired. The blood pressure was 130 systolic and 80 diastolic. The spinal fluid was normal.

Autopsy revealed a symmetrical enlargement of the thyroid with a hard nodule over the isthmus. Discrete lymphnodes were palpable on both sides of the neck and in the inguinal regions. The thymus was large, measuring 9 by 4 by 4 cm. On section, a tumor-like mass was seen, with a hard, partly calcified capsule, and a red, pulpy center. The mass measured 6 by 4 by 4 cm. A similar nodule was situated above the isthmus of the thyroid, measuring 25 by 22 by 13 mm. The thyroid was fleshy and firm. On cross-section, the left lobe contained a nodule, 14 by 10 by 10 mm. The heart weighed 220 Gm. The aorta measured 3.5 cm in circumference. On gross examination, the brain and cord revealed nothing unusual. The uterus and ovaries were infantile.

Microscopic section of the thymus mass showed hyperplasia of thymic tissue with a few large Hassall bodies. In most areas large, pale, epithelial cells predominated, in others small round cells. There was irregular fibrosis with marked hyalinization, particularly in the capsule. The second nodule above the isthmus of the thyroid was similar morphologically. Sections of the thyroid showed a diffuse epithelial hyperplasia. The colloid secretion was diminished. The stroma was increased and contained diffuse lymphocytic infiltration. The circumscribed nodule consisted essentially of epithelial-like cells. Sections of the heart and the muscles and those of the tongue and the muscles of the neck showed some lymphocytic infiltration and atrophy of the striated fibers.

The pathologic observations indicated extensive constitutional changes. The most conspicuous features were the multiple tumor-like nodules of thymus and thyroid, the small heart and narrow aorta, general lymphadenopathy and lymphoid infiltration of the muscles of the neck.

#### DISCUSSION

**JAMES EWING** I find it difficult to form any definite conclusion regarding the significance of the lesions in the thymus and the thyroid. Their interpretation would require much more careful study than I am able to make, even from this full report. The suggestion that the whole condition in this case is a phase of status lymphaticus is most interesting. I should like to ask Dr. Alter if he has some computation of the number of cases of myasthenia gravis reported in which there were such definite signs of status lymphaticus. In this case, these signs seem to be extremely well marked.

**HARRISON S. MARTLAND** Did the spleen and intestinal tract show a marked increase in lymphoid tissue?

**NICHOLAS ALTER** Yes, there was a large amount. With reference to Dr. Ewing's remark, there was not a single definite report emphasizing the presence of status lymphaticus. In some cases the thymus is described as enlarged, but the authors do not refer to the other requirements for status lymphaticus. Neither is there any investigation of the nature of the enlargement of the thymus, except for Bell's work in 1912, this author tried to classify some other cases and his own as benign thymoma. There is no mention of the concept of these nodules as infectious granulomas.

#### ERYTHROBLASTEMIA OF INFANTS, A STUDY OF SO-CALLED VON JAKSCH'S ANEMIA B. R. WHITCHER

Recently, cases of so-called von Jaksch's anemia have come to be regarded as belonging to the regularly accepted groups of secondary anemias in children, or as



increase in amino nitrogen The increase in fermentable (true) sugar in blood after hydrolysis by amylase ranged from 9 to 29 mg per hundred cubic centimeters of blood as dextrose

The fact that the combined sugar cannot be demonstrated in the protein-free blood filtrate suggests that it is chemically combined with blood proteins and may be present in the blood as "gluco protein"—sugar combined with blood protein in a glucoside linkage

The nonfermentable reducing substance in human blood averaged 25 mg per hundred cubic centimeters as dextrose

#### A CASE OF PAROXYSMAL TACHYCARDIA IN THE COURSE OF ACTIVE SUBACUTE BACTERIAL ENDOCARDITIS ARTHUR N FOXE

A man, aged 23, had an essentially unimportant history The onset of the illness occurred two months before admission with a cold, cough and blood-streaked sputum Several weeks later he was feverish and had night sweats and pain in the left loin and joints Physical examination showed evidences of mitral stenosis The general features led to a diagnosis of subacute bacterial endocarditis, which was confirmed by a positive blood culture for *Streptococcus viridans* The subsequent course was febrile, with numerous peripheral, visceral and cranial embolic phenomena Two weeks before death an attack of paroxysmal auricular tachycardia began, the pulse rate being 188 The attack lasted for six days During the illness, the patient received doses of digitalis and occasional hypnotics Death was due to cerebral complications

Postmortem examination showed petechiae of the skin and conjunctivae, petechiae of the pleura, left hemohydrothorax and hydropericardium, both unusual in this disease There were auricular and interauricular septal myocardial petechiae, mitral and aortic valvular and mural endocarditis, and infarctions of the spleen and kidneys Microscopic examination showed myocardial petechiae, as observed, focal fibrotic myocardial change and one large focal accumulation of monothelial cells in the ventricular myocardium

Cardiac arrhythmias are said to be rare in active subacute bacterial endocarditis. Bickel could find no case in the literature, he described a case of heart block Rothschild, Sachs and Libman described the only other case that I have been able to find in the literature, that of a patient with auricular fibrillation Myocardial involvement is often said to be rare in this disease Blumen found active inflammatory changes in 1 per cent of the cases, Clawson in 24 per cent and Thayer in 61 per cent

The discrepancies in the studies cited and the difference between apparent fact and the valid view of Mackenzie, that myocardial involvement is usually present when there is an active endocarditis, are strange For a better clinical and pathologic understanding of the disease, it is essential that these opposing views be estimated correctly Symptomatically, clinically and pathologically, there are barriers to the knowledge of the myocardial involvement in subacute bacterial endocarditis "These patients," as Debre accurately stated, "are cachectics, never cardiacs" The anemia and the peripheral embolic phenomena are so striking and varied that they attract almost the entire attention of the clinician This is fairly different from the monotonous regularity of the congestive phenomena of chronic cardiovalvular disease, in which the heart signs and close digitalis control become so engaging Pathologically, the endocardial manifestations so obtrude that one largely neglects a more careful study of the myocardium It is probable that when the studies of the living and dead myocardium in subacute bacterial endocarditis have been pursued with the persistence with which those of the presystolic murmur and the Aschoff body in acute rheumatic fever have been pursued, one will find little, if any, disparity in the frequency of myocardial involvement in the two diseases The report of this case is a small effort in that field

splenic lymph nodes stood out prominently and were considerably enlarged and hyperemic. The spleen was from two to three times larger than normal. The lungs, heart, liver and other organs showed no distinctive gross pathologic changes. Microscopically, the tonsils and the lymphoid tissue of the mesentery showed characteristic simple "myeloid" hyperplasia. Microscopically, the spleen showed a diminution in the number and size of the lymphoid follicles. On first impression, the splenic pulp suggested marked hyperemia of the sinuses. On further examination, the exact structure of the splenic pulp had not been established. The microscopic changes in the bone-marrow had not yet been studied. The remaining viscera showed no pathologic features microscopically. An examination of the blood made before death showed hemoglobin, 26 per cent (Dare), red blood cells, 1,750,000, and index, 0.7. The cells showed poikilocytosis and polychromatophilia, and erythroblasts were present. The white blood cells numbered 94,400, with a differential count of neutrophils, 51 per cent, lymphocytes, 36 per cent, and myelocytes 13 per cent.

There are several similar features in the two cases reported by Dr. Whitcher and in my case that came to autopsy. A striking feature is the peculiar pigmentation of the skin which at the time of autopsy suggested marked hemolysis. It is of interest to consider whether my case may not present the pathologic aspects of Dr. Whitcher's cases. All three of these cases appear to be characterized by primary diminution in the number of red cells, associated with the presence of immature red cells in the circulating blood, together with leukocytic changes suggesting those of leukemia. In my case the myeloid hyperplasia of the tonsils and of the mesenteric nodes is of interest in relation to the possible leukemic changes. The histologic picture of the spleen suggests a possible deficiency of its hematopoietic function. This condition, therefore, would appear to be one of primary erythrocytogenic failure with associated myeloid hyperplasia. If the term "pseudoleukemia" is defined as a primary systemic lymphoid hyperplasia without an associated lymphocytic blood picture of leukemia, it could be ruled out in these cases, the predominant and apparently primary if not definitive change being an erythrocytogenic deficiency.

NICHOLAS M. ALTER. I have seen Dr. Whitcher's slides, which were stained by MacNeal's method. This produces marked contrast which does not give much possibility for mistake. The drawings do not do justice to it. The picture is striking, and it shows at times a more marked condition than in pernicious anemia.

B. R. WHITCHER. Some time after having seen these two or three children, a premature infant, a girl, was born at about 7 months in the Babies' Ward, and died at the age of 19 days. I made a blood count, and found more than 300 nucleated red cells to 100 leukocytes. In premature infants, born at 7 or 8 months, one does find a large number of these nucleated red cells, but rarely in an infant born at full term, the infants whose cases I reported were all born at full term.

HARRISON S. MARTLAND. How about the icteric index?

B. R. WHITCHER. I did not determine the icteric index. I had two cases in brothers, who had hemolytic icterus, and each had a splenectomy and made a good recovery, they are now normal. Before operation smears showed some nucleated red cells with some polychromatophilia, but not nearly as many nucleated red cells as those of the three cases reported.

#### A STUDY OF COMBINED CARBOHYDRATE IN THE BLOOD. ICHIRO KATAYAMA (by invitation)

The protein of the blood, which had been freed from sugar, when heated with second-normal hydrochloric acid in a bath of boiling water for two hours, yielded a substance giving the typical reduction of alkaline copper solutions. With phenylhydrazine, an osazone was obtained which corresponded with the glucozazone. Combined sugar is present in greater amount in the plasma than in the corpuscles.

The blood was incubated for four hours at 40 C., with 0.3 per cent amylase solution and showed a marked increase in reducing substances with a much greater

of a single population, but offers exact material for the comparison of the human races with one another

The problem of inferiority is taken up by Max Berliner. Inferior forms of persons (Kuemmerformen) are those who do not reach the height of development which is characteristic of their race. The conception of inferior forms has been introduced by F. von Kraus and T. Brugsch and is apt to replace so-called infantilism. Inferiority, which in this connection is used merely from a morphologic standpoint, may affect the whole organism or parts of it. For clinical purposes, Berliner distinguishes the following forms of inferiority: (1) forms associated with diseases of the glands of internal secretion and with anomalies of the skeleton, to which group belong hypophyseary dwarfism, dyscerebral dwarfism, mongolism, cretinism, and myxedema, (2) forms with predominating changes of the skeleton, such as rickets, chondrodystrophia, osteopsathyrosis, enchondromas and Moeller-Barlow's disease, and (3) dystrophic forms.

The chapter on the individual development in infancy and childhood by A. Schlossmann and A. Eckstein is short and contains little of value.

The seventh issue contains, besides chapters on childhood, puberty and senility by M. Berliner and on the changing judgment concerning the artistic forms of the human body by Eugen Hollander, a contribution by Georg W. Schorr in which pathologists will be much interested. This contribution deals with the significance of thanatology for the biology of the person. Thanatology is the science of death. Those whose duty it is to explain the occurrence of death on the basis of anatomic observations often fail to explain why death has occurred at a certain moment and not hours or days before or afterward. Death does not result from a single cause, but is the outcome of a series of conditions which are incompatible with life. It is often impossible to determine all these conditions after life has vanished, and the work at the necropsy table necessarily has to be completed by studies immediately before and during death.

**LABORATORY TECHNIQUE. THE METHODS EMPLOYED AT ST. LUKE'S HOSPITAL, NEW YORK.** F. C. WOOD, KARL VOGEL and L. W. FAMULENER. Third edition, revised and enlarged. Price, \$3.75. Pp. 318. New York: James J. Dougherty, 1929.

The first edition appeared in 1917. Since then a great increase has taken place in the demands on the clinical laboratory necessitating a thorough revision in order to reflect adequately present practice. There are three sections: histologic methods by F. C. Wood, 20 pages; clinical pathology and clinical analytic methods by Karl Vogel, 100 pages; and bacteriology including serology by L. W. Famulener, 184 pages. The book lays no claim to being a complete guide to all laboratory methods; Kahn's test for syphilis, for instance, is not mentioned. The methods described are those used in St. Luke's Hospital in New York, and "preference is given to methods that appear to be most reliable at the same time as they are practical." The book is an eminently safe technical guide so far as it goes and of interest to all workers in clinical laboratories as an illustration of the actual practice in a large hospital.

## Book Reviews

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DIE BIOLOGIE DER PERSON EIN HANDBUCH DER ALLGEMEINEN UND SPIZIELLEN KONSTITUTIONSLEHRE UND MITARBEIT ZAHLREICHER FACHMANNER  
Herausgegeben von PROF DR T BRUGSCH und PROF DR F H LEWY  
Parts 4-7 Berlin Urban & Schwarzenberg, 1926 and 1927

The first volume of this work was reviewed in the ARCHIVES (4 151, 1927). The fourth issue of the great system of the biology of the person brings an excellent contribution by E. Keeser on the relations between constitution and action of drugs. In collaboration with Joachimoglu the author has done pioneer work in this new field of constitutional and pharmacodynamic research which offers many possibilities for further investigations, especially with regard to idiosyncrasy. Not only does constitution influence the action of drugs, but also drugs when given for a long period of time influence the constitution. After a general discussion of the internal and external factors that determine the effect of a drug on a given individual, Keeser takes up the various chemical substances in detail. Though the discussion is brief, one will find many valuable suggestions especially in the paragraphs on alcohol, anesthetics, alkaloids, hypnotics and organic and inorganic poisons. A discussion of industrial poisonings is also given.

The next chapter is devoted to the question of constitution and the abuse of narcotics. Ernst Joel and Fritz Fraenkel try to cover this intricate problem in forty-two pages and succeed well, though some of their discussions are rather superficial. As far as prohibition is concerned, the authors come to the conclusion that its advantages by far excel its disadvantages.

Using statistical data as a basis, G. Florschuetz speaks of the great importance of the constitution in calculating the risk of life insurance.

Robert Heindl points out that a tremendous material for constitutional research has accumulated in the archives of the identification services of the various nations. This material has the great advantage that it is based on uniform and exact methods, and that it not only contains the measurements, photographs and fingerprints of millions of people, but also gives an account of the story of their life and of their mental and moral qualities. Heindl describes in detail the methods of anthropometry as applied for criminalistic purposes, and of the portrait parlé introduced by Bertillon. It is interesting to learn that some of the modern criminalistic methods were used already in ancient times, and that a warrant issued at Alexandria in 145 B.C. read very much up to date. The study of Heindl's paper can be highly recommended.

The greater part of the fifth issue is devoted to the factors which determine the person's fitness for life. Carl Coerper takes up the question from the somatic and W. Peters from the psychologic point of view. When the time comes that a young person has to choose his future occupation, not only his inclination but his constitution should be taken into consideration, if this is done, much disappointment and despair can be avoided. The physician well trained in the science of constitution should have a leading position among those who deal with problems of occupation.

In the same issue, Coerper also discusses constitution in relation to sport. Every person has an inclination for a certain kind of exercise which determines his favored sport. If sport is to be healthful, it should be adjusted to the person's constitution.

In issue six, Brugsch gives a complete presentation of the morphology of the person. He describes the different types as advanced especially by the French school and devotes much space to the methods of anthropometry, following the work of R. Martin. Mathematical measurements eliminate subjectivity in judgment, and uniformly applied not only make possible the study of the constitutional types

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## Books Received

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PRINCIPLES OF PATHOLOGY FOR PRACTITIONERS AND STUDENTS By H D'Arcy Power, M D, F R P S, Professor of Pathology, College of Physicians and Surgeons, San Francisco, and William W Hala, M D, Assistant Professor of Pathology, Long Island College Hospital, Brooklyn, N Y Price, \$10 Pp 787, with 298 illustrations New York D Appleton and Company, 1929

DISEASES OF THE THYROID GLAND By Arthur E Hertzler, M D, Surgeon to the Halstead Hospital With a chapter on Hospital Management of Goiter Patients by Victor E Chesky, M D, Associate Surgeon to Halstead Hospital Price, \$7 50 Pp 286 Second edition, entirely rewritten St Louis C V Mosby Company, 1929

ARBETEN FRÅN KAROLINSKA INSTITUTETS PATOLOGISKA AVDELNING UTGIVNA AV FOI KE HENSCHEN Volume 4, 1928 Professor i patologisk anatomi Stockholm, 1929

A CONTRIBUTION TO THE KNOWLEDGE OF LYMPHOGRANULOMA INGUINALE By Sven Hellerstrom, Lic Med From the Pathological Department (Head Professor F Henschen), and the Dermato-Venereological Clinic (Head Professor J Almkvist), of the Caroline Institute Pp 224, with 16 illustrations Stockholm P A Norstedt & Soner, 1929

This is a complete and well illustrated presentation of the present knowledge concerning inguinale lymphogranuloma Forty-seven carefully studied cases are reported The bibliography contains 229 references The main points in the author's summary will be given in abstracts from the current literature

THE ORIGIN OF MALIGNANT TUMORS By Theodor Boveri, University of Wurzburg Translated from German by Marcella Boveri, with a foreword by Maynard M Metcalf, Johns Hopkins University Cloth Price, \$2 50 Pp 128 Baltimore Williams & Wilkins Company, 1929

REPORT OF THE LABORATORY AND MUSEUM OF COMPARATIVE PATHOLOGY OF THE ZOOLOGICAL SOCIETY OF PHILADELPHIA By Herbert Fox, M D, Pathologist Pp 65 1929

This report contains interesting notes on diseases of various kinds of animals

DIE BIOLOGIE DER PERSON Ein Handbuch der allgemeinen und speziellen Konstitutionslehre unter Mitarbeit zahlreicher Fachmanner Volume 4 Von Prof Dr T Brugsch und Prof Dr F H Lewy Price, 13 marks Pp 825-986 Berlin Urban and Schwarzenberg, 1929

THE FORTY-FOURTH ANNUAL MEDICAL REPORT OF THE TRUDEAU SANATORIUM AND THE TWENTY-FOURTH MEDICAL SUPPLEMENT FOR THE YEAR ENDING SEPTEMBER 30, 1928 Together with the Twelfth Collection of the Studies of the Edward L Trudeau Foundation for Research and Teaching in Tuberculosis Price, 50 cents Pp 257 Trudeau, N Y, 1928

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